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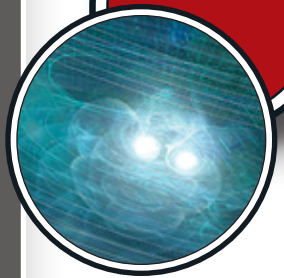

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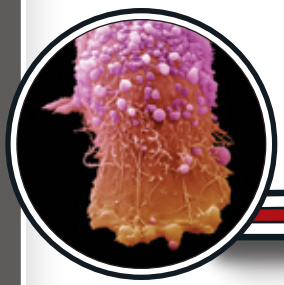
Have Humans Altered the Earth Forever?

Clues to Zika's Virulence



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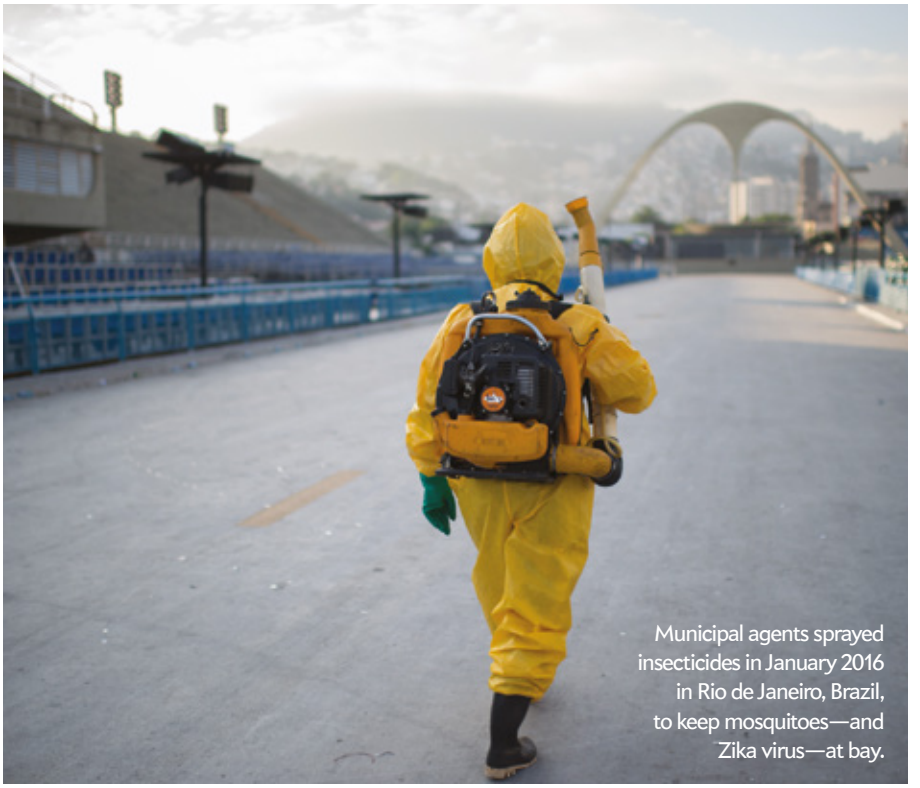

Municipal agents sprayed insecticides in January 2016 in Rio de Janeiro, Brazil, to keep mosquitoes—and Zika virus—at bay.

FROM THE EDITOR

The Year in Science

In 2016 scientists made a discovery sure to usher in a new era of physics: for the first time, they detected gravitational waves—ripples in the fabric of space predicted by Albert Einstein 100 years ago. Meanwhile the Zika virus, after lying low for nearly 70 years, mounted an aggressive global attack. Climate change aggravated social crises in the Middle East, contributing to a mass exodus of refugees. *Scientific American* covered all these events in print or on digital platforms. In this special collection, you'll find those stories (*pages 30, 52 and 98*) and more.

To choose the articles in this volume, my colleagues and I polled our editors for their favorite pieces and compiled the stories and events that drew the greatest attention of our readers and the world. We selected the most important news in science, of course, but also included entries that were particularly compelling reads, such as one that describes dramatic advances in treating cancer by inducing the immune system to attack tumors (*page 44*) and another that muses on whether we might actually be living in a computer simulation (*page 84*). Science moves fast, and so, where needed, we have updated facts or added an editor's note highlighting major new developments. For example, just a few short months after we reported the detection of gravitational waves in February, physicists detected gravitational waves for the second time.

The stories that follow cover the gamut from the smallest machines (*page 72*) to the biggest structures in space (*page 14*), from technology that promises hands-free driving (*page 78*) to tools capable of altering human evolution (*page 64*). If you read no other articles about science from 2016, read these.

Andrea Gawrylewski
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TOP SCIENCE STORIES OF 2016

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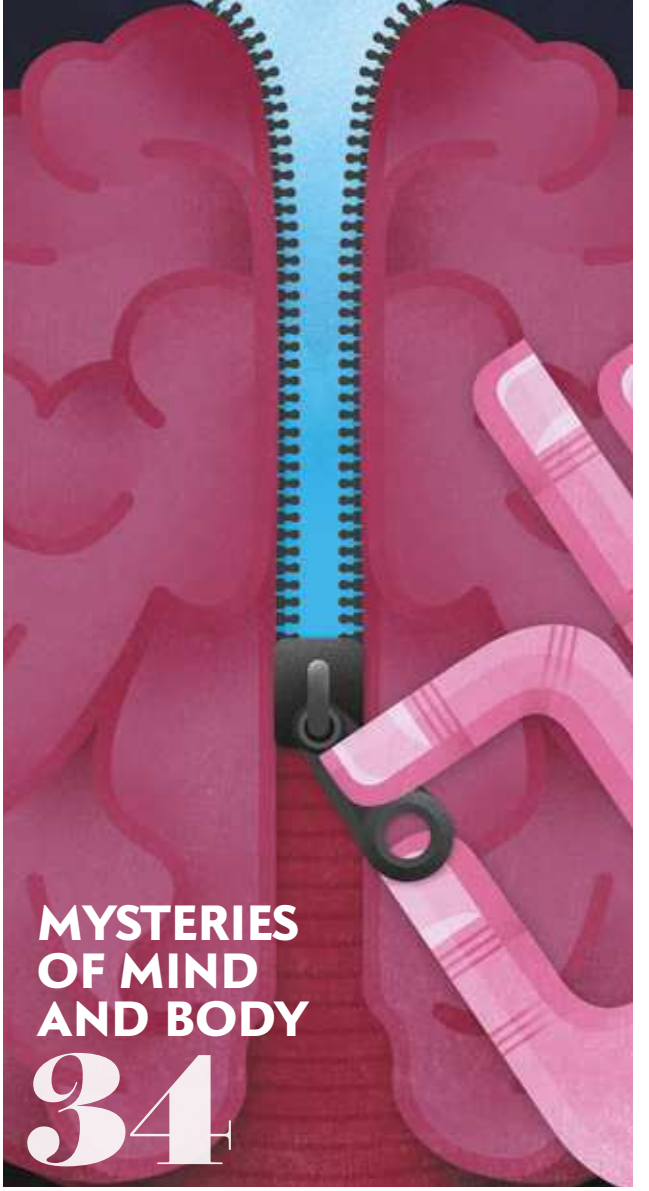

6 The Search for Planet X
In the far reaches of the solar system, a hidden planet larger than Earth may be lurking. *By Michael D. Lemonick*

14 Our Place in the Cosmos
The Milky Way turns out to be part of a massive supercluster of galaxies that forms one of the largest known structures in the universe. This discovery is only the beginning of a new effort to map the cosmos. *By Noam I. Libeskind and R. Brent Tully*

22 The Emptiest Place in Space
Efforts to explain a strange cold spot in the cosmos have led to the discovery of something even odder: a vast area with very little matter. *By István Szapudi*

30 Ripples in Spacetime
In February, scientists announced that a daring experiment had finally confirmed Einstein's 1916 prediction of gravitational waves. *By Clara Moskowitz*

36 Where Am I? Where Am I Going?
Neuroscientists are discovering how the brain navigates. *By May-Britt Moser and Edvard I. Moser*

44 The Cancer Defense
Enhancing the body's own immune system is leading to promising results in the battle against malignancy. *By Karen Weintraub*

52 How Zika Spiraled Out of Control
Our reporter goes into the lab to see how investigators are gathering clues to Zika's sudden spread around the world. *By Dina Fine Maron*

58 Living to 120
Drugs already used for some medical conditions are surprisingly good at keeping aging cells healthy. They offer new hope for developing medicines able to slow aging. *By Bill Gifford*

64 The Red Line
Researchers are on the threshold of crossing a sharp ethical line: permanently altering the human genetic code. *By Stephen S. Hall*

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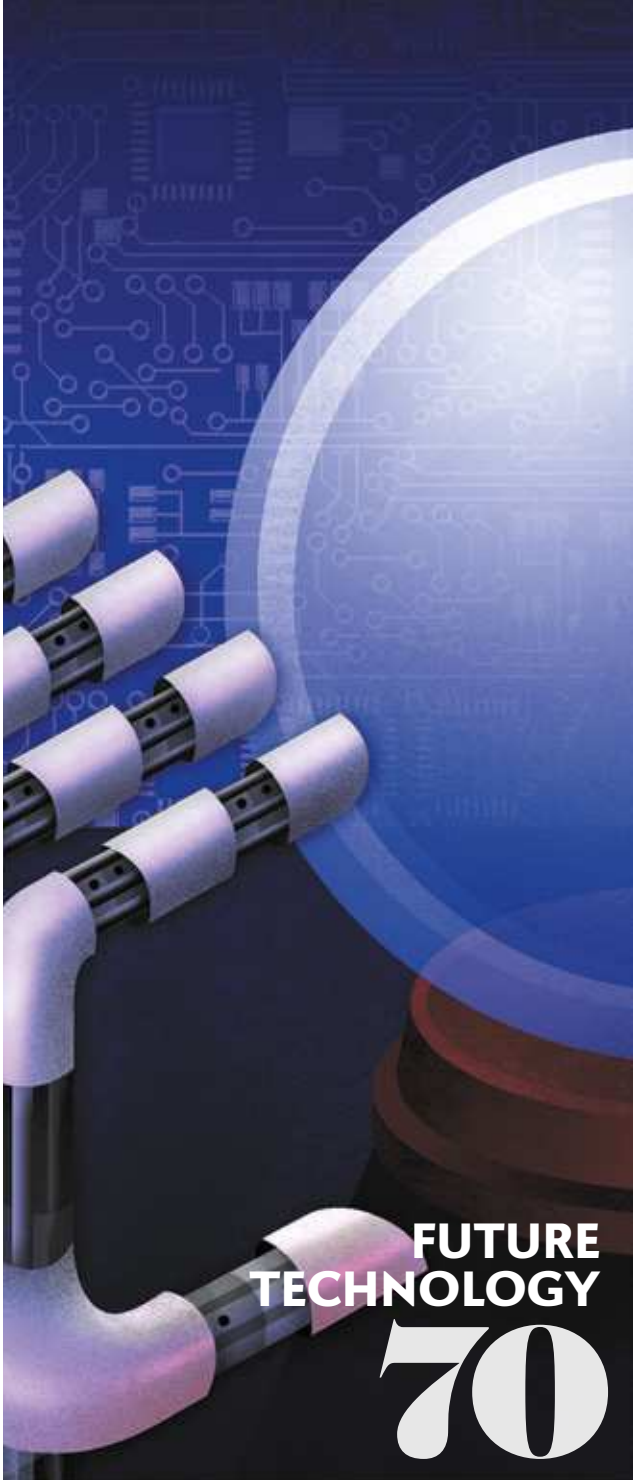

72 Machine Life
Synthetic biologists are close to putting living cells to work diagnosing human diseases and repairing environmental damage.
By Timothy K. Lu and Oliver Purcell

78 The Truth about "Self-Driving" Cars
They are coming, but not the way you may have been led to think. *By Steven E. Shladover*

84 Are We Living in a Computer Simulation?
High-profile physicists and philosophers gathered earlier this year to debate whether we are real or virtual.
By Clara Moskowitz

88 Mystery Human
An astonishing trove of fossils has scientists, and the media, in a tizzy over our origins. *By Kate Wong*

98 Syria's Climate Refugees
Farmers who have escaped the embattled nation explain how drought and government abuse are driving social violence. *By John Wendle*

104 A History in Layers
Humans are profoundly altering the earth. Is our impact enough to matter across geologic time? Some say it is. Welcome to the Anthropocene. *By Jan Zalasiewicz*

DEPARTMENTS

1 FROM THE EDITOR: The Year in Science

112 END NOTE: The Circle of Life

Articles in this special issue are updated or adapted from previous issues of *Scientific American* and from ScientificAmerican.com.
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COSMIC WONDERS

Four recent findings have redefined our place in space, revealing that the cosmic universe we find ourselves in is vaster, stranger and altogether more wondrous than we had known. On page 6, "The Search for Planet X" describes the mounting evidence that a "super Earth" up to 10 times as massive as our own world may lurk beyond Pluto. "Our Place in the Cosmos" (*page 14*) depicts one of the largest known structures in the universe—an extraordinarily giant conglomerate of galaxies that includes our own Milky Way. "The Emptiest Place in Space" (*page 22*) recounts the recent discovery, farther out, of a "supervoid" extending 1.8 billion light-years across that is surprisingly devoid of matter. And in one of the most talked-about findings of the year, scientists are viewing our cosmic surroundings with a new set of eyes thanks to the first detection of gravitational waves—products of colliding black holes (*page 30*).

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SEVERAL STRANGE BODIES in the Kuiper belt beyond Neptune suggest the possible presence of an unseen large planet, which could even have a moon of its own.

TOP SCIENCE STORIES OF 2016

SPACE

THE SEARCH

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FOR PLANET X

In the far reaches of the solar system, a hidden planet larger than Earth may be lurking

By Michael D. Lemonick

Illustration by Ron Miller

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SOMETHING VERY ODD SEEMS TO BE GOING ON OUT BEYOND PLUTO. ASTRONOMERS have known for more than two decades that the tiny former planet is not alone at the edge of the solar system: it is part of a vast cloud of icy objects known collectively as the Kuiper belt. But unlike most of their fellow travelers, and unlike the planets and most asteroids, which orbit between Mars and Jupiter, a small handful of Kuiper belt objects, or KBOs, have orbits that are decidedly weird. For one thing, they take unusually elongated paths around the sun, unlike the roughly circular orbits of most planetary bodies.

These badly behaving objects, which number between four and a dozen, depending on who is counting, share another orbital peculiarity as well. Like most KBOs, they orbit at an angle to the pancake-shaped plane where the planets live, rising above the pancake for part of the time, then plunging through to dip below for the rest. But unlike their frozen brethren, these objects all pass through the planetary plane at the same time that they make their closest swing toward the sun.

Or, to use a term even many astronomers find arcane, they have remarkably similar arguments of perihelion (AOP). "Normally," says Scott Sheppard, a planetary scientist at the Carnegie Institution for Science, "you would expect the arguments of perihelion to have been randomized over the life of the solar system." Maybe it is just a coincidence that these few bodies ended up with the same AOP: such a thing should happen, purely by chance, less than a few percent of the time. Those odds are something like getting 10 heads in a row when you flip a coin: pretty unusual but nowhere near impossible.

But those 10 heads could also mean your coin is loaded, and the same goes for these KBOs. Something may have forced the objects into this strange configuration—and that something could be a huge, unknown planet, significantly more massive than Earth, lurking out at the edge of the solar system: a super Earth (super Earths are planets up to roughly 10 times more massive than Earth). If such a hidden object—sometimes whimsically called "Planet X"—exists, it would orbit at least 10 times farther from the sun than Neptune—too distant and too faint to have been spotted by any telescope to date. Yet its sizable mass would have gravitational effects on the rest of the solar system—effects that might explain the odd orbits astronomers have seen.

"We don't have definitive proof yet that there's a planetary-mass body out there," says Nathan Kaib, a planet-formation theorist now at the University of Oklahoma. "But something funny is going on that we don't understand." And a growing number of astronomers are putting stock in the once ridiculed notion of the presence of a super Earth in our midst, Planet X.

As Kaib suggests, the evidence for a hidden planet is far from ironclad. Many astronomers still doubt the idea, and even those who invoke it as a possibility say they are not yet fully convinced. The history of astronomy is full of invisible mystery planets, their existence inferred from the peculiar orbits of other objects. Some have turned out to be major discoveries. Others were false alarms. It may be that we do not know our solar system nearly as well as we thought we did. If there is a Planet X out there, it will necessitate a wholesale rewriting of some key chapters of the solar system's history.

IN BRIEF

A number of distant, icy objects circling the sun with weird orbits have led some scientists to suspect there may be more planets than we know of in the solar system.

The evidence, they say, supports the idea that one or more "super Earths"—planets that are up to 10 times more massive than Earth—may orbit far beyond Neptune.

These bodies would be too far and dim to have shown up in any existing telescope, but future observatories may be able to spot them, if they are out there.

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ON THE TRAIL OF HIDDEN WORLDS

THE FIRST SEARCH for a hidden planet circling the sun came in the early 1800s, when scientists became increasingly convinced that Uranus, discovered accidentally in 1781 by the musician-turned-astronomer William Herschel, was not orbiting quite as Newton's law of gravity said it should. Several scientists posited that the gravity of a large, undiscovered planet was to blame—and in 1846 German astronomer Johan Galle spied the gas giant Neptune, basically where his French colleague Urbain Le Verrier had calculated it should be. (There is good evidence that Galileo had actually seen Neptune as early as 1612 with his small, crude telescope but had assumed it was a star.)

In the early 1900s Boston aristocrat Percival Lowell began a search for another hidden planet based at his own personal observatory in Flagstaff, Ariz. This time the evidence came in the form of anomalies in the orbits of both Uranus and Neptune, pointing to the existence of yet another unseen giant planet. Early in 1930 a young assistant at Lowell Observatory named Clyde Tombaugh found a planet more or less where the calculations said it should be—a replay of the discovery of Neptune. "The Sphere, Possibly Larger than Jupiter and 4,000,000,000 Miles Away, Meets Predictions," the *New York Times* announced on March 14, 1930.

THE HISTORY OF ASTRONOMY IS FULL OF INVISIBLE MYSTERY PLANETS, THEIR EXISTENCE INFERRED FROM THE PECULIAR ORBITS OF OTHER OBJECTS.

It did not, though. Within a few decades it became clear that Pluto is far from Jupiter's size and is actually smaller than Earth's moon. Its meager gravity could not possibly explain anomalies in the orbits of Neptune and Uranus—which turned out to be just as well because those anomalies faded away on further inspection. In that sense, Pluto was a false alarm.

In the big picture, however, its discovery was extraordinarily important. By the 1980s planetary scientists had begun to suspect that Pluto was not a puny planet orbiting all alone in the solar system's frozen outskirts but simply the brightest member of a vast, richly populated region known as the Kuiper belt. In 1992 the first KBO (besides Pluto, that is) was spotted with a telescope in Hawaii, and since then, observers have tallied another 1,500 or so. The 2005 discovery of Eris, which rivals Pluto in size and significantly outweighs it, threatened to open a floodgate that could have added several more planets to the existing roster of nine. That specter prompted the International Astronomical Union to demote Pluto from planet to dwarf planet in 2006.

RESHUFFLING THE SOLAR SYSTEM

THE DISCOVERY of the Kuiper belt, in turn, lends credence to the latest search for a Planet X because it helps explain how such an object might have ended up so far from the sun that we still have not seen it. Computer simulations suggest that the icy bodies of the Kuiper belt should have formed somewhere in the neighborhood Neptune now occupies. Something must have flung them much farther out (or scattered them, to use the technical term) to their present positions. This observation led astronomers to theorize that a disruption took place during a chaotic period soon after the nascent planets congealed from the "protoplanetary disk" of gas and dust that swirled around the newborn sun. During this unsettled time, Jupiter, Saturn, Uranus and Neptune most likely shifted by hundreds of millions of kilometers from their initial orbits, their gravity sending the KBOs flying outward. Some simulations even point to the existence of a possible fifth gas giant that was ejected from the solar system entirely as the others adjusted their positions.

It is easily plausible that if a super Earth existed, it, too, could have been flung outward during this period of general mayhem. And because super Earths have proved to be common among the roughly 2,000 exoplanets discovered around other stars over the past couple of decades, it is also reasonable to suppose that there could once have been one circling our own sun. With that in mind, says Ben Bromley of the University of Utah, who collaborated with Scott Kenyon of the Harvard-Smithsonian Center for Astrophysics, "we ran some mock-ups of what would happen to a super Earth scattered from the region where Jupiter and Saturn are today." In most cases, they found that the super Earth would be flung into a highly elliptical orbit, which would gradually become more and more stretched out until the planet was ejected from the solar system entirely. But if the scattering happened early enough—within about 10 million years after the formation of the planets, before the protoplanetary gas dissipated, Bromley says, "the super Earth could interact with the gas [gravitationally] and settle out in the boondocks in a more or less circular orbit."

That scenario is one way to make the kind of massive Planet X that Lowell set out to find in the early 1900s and the kind Galle and Le Verrier did find when they collaborated to discover Neptune half a century earlier. Another way to do it, Kenyon and Bromley found, was for the super Earth to form in place at perhaps 200 astronomical units (AU) from the sun, which is to say, 200 times the sun-Earth distance of 93 million miles. (Neptune, in contrast, orbits at about 30 AU from the sun.) Such in situ formation would be possible only if there were sufficient planet-forming material—pebble-size bits of rock and ice—orbiting out that far.

There is no direct evidence that this was ever the case in our own solar system, but there is quite good evidence that it happens with stars that are very much like the sun. "If you look at nearby solar-type stars," however, Kenyon says, "some of them have these debris disks with material extending to 200-ish AU away from the star itself. So it wouldn't be unprecedented." And although there is no proof that super Earths have formed at such a distance around these nearby stars, he says, "at least you have the basic ingredients." All these simulations were purely speculative when Kenyon and Bromley began working on them a decade or so ago. Nobody had seen even a hint that a super Earth was actually out there.

ENTER SEDNA

THAT SITUATION began to change with Sedna. In 2003 Mike Brown of the California Institute of Technology, along with two colleagues, observed what was perhaps the strangest solar system object ever discovered up until that point. It was an icy body, now estimated to be about 1,000 kilometers across, and similar in many ways to Pluto, Eris and other KBOs. Its orbit, however, had not been seen before. Sedna never comes closer than 76 AU from the sun, or more than twice as far away as Neptune, on its highly elongated 11,400-year orbit, and it retreats to more than 930 AU—31 times as far as Neptune—at its most distant.

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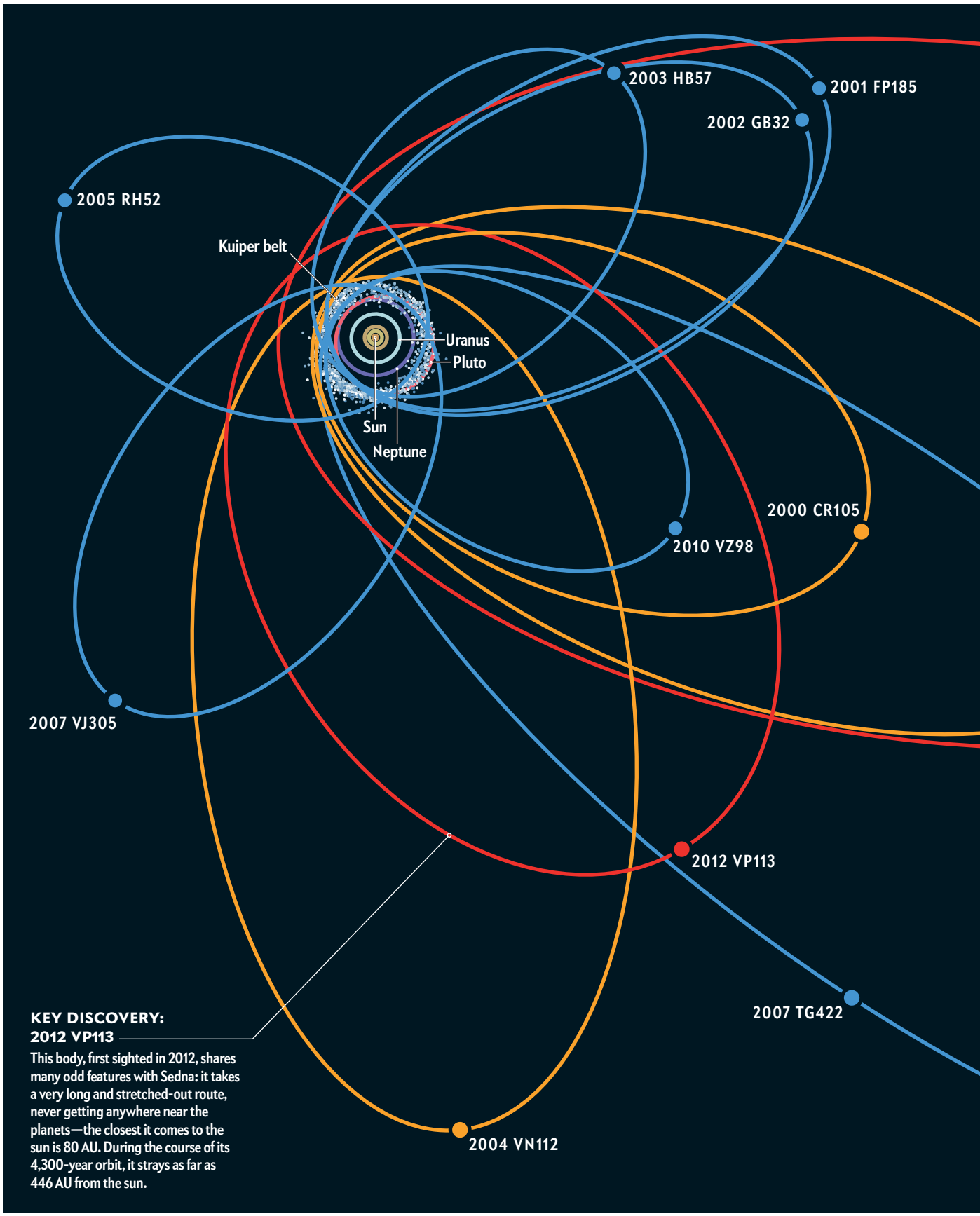
2003 HB57
2001 FP185
2002 GB32
2005 RH52
Kuiper belt
Uranus
Pluto
Sun
Neptune
2000 CR105
2010 VZ98
2007 VJ305
2012 VP113
2007 TG422
2004 VN112
KEY DISCOVERY:
2012 VP113
This body, first sighted in 2012, shares many odd features with Sedna: it takes a very long and stretched-out route, never getting anywhere near the planets—the closest it comes to the sun is 80 AU. During the course of its 4,300-year orbit, it strays as far as 446 AU from the sun.

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Extreme Outer Objects

Far beyond the eight planets, the asteroid belt and even the distant Kuiper belt past Neptune, astronomers have seen roughly a dozen objects moving in strange orbits. These icy bodies all take elongated paths around the sun, and they share an odd feature—they seem to make their closest approach to the sun around the time that they cross the plane of the planets. One reason scientists suspect the presence of a large hidden planet, a so-called super Earth, in the far reaches of the solar system is that the gravitational pull of such a planet could account for these bodies' synchronized behavior.

10 OTHER NOTABLE EXTREMES

Astronomers have observed at least 10 other bodies that share some features with Sedna and 2012 VP113, such as an oblong orbit and a path that crosses the plane of the planets as it makes its closest approach to the sun. They all have average distances from the sun of at least 150 AU and can be divided into three categories based on their perihelion, or closest approach to the sun: those that never come nearer than 50 AU (the "inner Oort cloud"), those that approach between 40 and 50 AU from the sun (the "extreme detached disk"), and the "extreme scattered disk" of objects that swing in between 30 and 40 AU.

Known Extreme Outer Solar System Objects

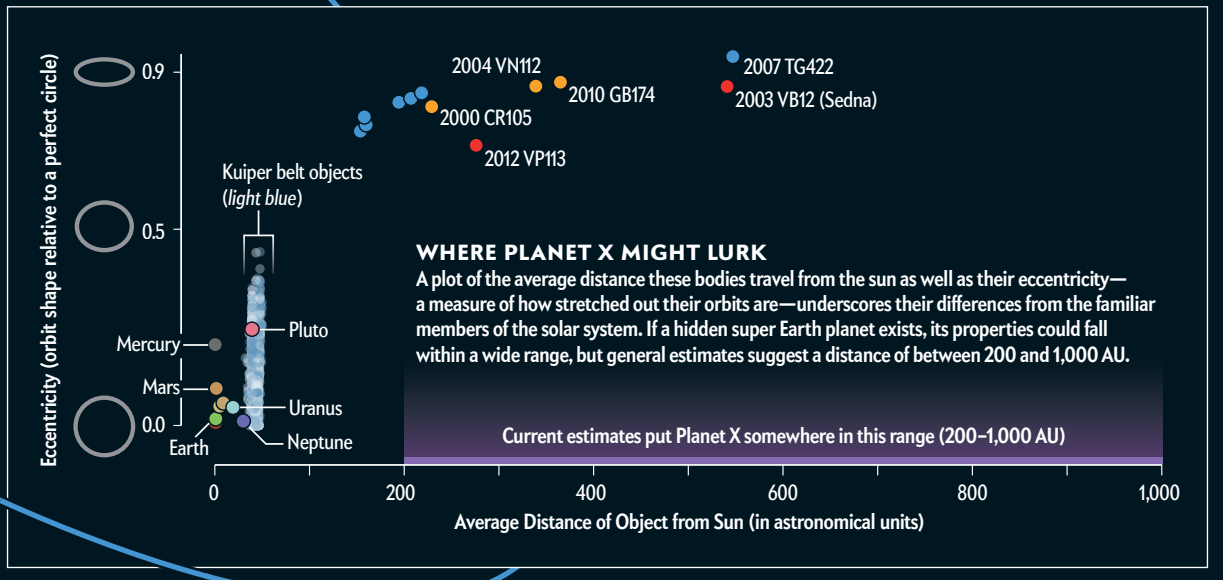
- Inner Oort cloud
- Extreme detached disk
- Extreme scattered disk

2003 VB12 (Sedna)

2010 GB174

KEY DISCOVERY: SEDNA

Discovered in 2003, Sedna is one of the most distant known objects in the solar system and has perhaps the oddest orbit ever seen. This icy rock, about 1,000 kilometers across, swings as far as 930 AU (the distance from Earth to the sun) from the center of the solar system and never comes closer than 76 AU in its 11,400-year oblong orbit.



WHERE PLANET X MIGHT LURK

A plot of the average distance these bodies travel from the sun as well as their eccentricity—a measure of how stretched out their orbits are—underscores their differences from the familiar members of the solar system. If a hidden super Earth planet exists, its properties could fall within a wide range, but general estimates suggest a distance of between 200 and 1,000 AU.

SOURCES: INTERNATIONAL ASTRONOMICAL UNION MINOR PLANET CENTER'S LIST OF TRANSNEPTUNIAN OBJECTS (*Kuiper belt object data*); SCOTT S. SHEPPARD *Carnegie Institution for Science (extreme outer solar system object data)*

Graphic by Jan Willem Tulp

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"Sedna was really surprising," says co-discoverer Chad Trujillo, now at Gemini Observatory in Hawaii, "because it was completely unexplained." Its stretched-out orbit resembled those of long-period comets, but unlike Sedna, these have one orbital end firmly anchored by the gravity of the giant planets. Sedna appeared unanchored to anything. "Nobody had thought an object like this could exist," Trujillo says, "and nobody had an explanation of how it got there."

Over the next decade or so observers found 10 other, smaller objects whose orbits are also elongated and that never come within shouting distance of Neptune. By itself, this was not especially noteworthy: none of them was nearly as extreme as Sedna either in the shape of its orbit or in how far beyond Neptune its perihelion came—that is, its closest approach to the sun. But all of them, along with Sedna itself, shared a similar argument of perihelion, the unusual orbital parameter that describes how far above or below the plane of the solar system an object is when it reaches perihelion. And that seemed … odd.

Things got significantly odder in 2014, when Trujillo and Sheppard announced in *Nature* that they had discovered a second Sedna-like object, about half as big as Sedna itself, after searching for something like it for a decade. "If you're a biologist," Trujillo says, "and you find some weird creature, you're pretty sure there's got to be more like it out there." Likewise in astronomy, he says—unless that first creature was a total fluke. "Maybe this one object happened to be thrown in this orbit for reasons we don't understand," he says, "but you don't really know until you find another one." Now they had.

"NOBODY HAD THOUGHT AN OBJECT LIKE THIS COULD EXIST," CHAD TRUJILLO SAYS, "AND NOBODY HAD AN EXPLANATION OF HOW IT GOT THERE."

Known provisionally as 2012 VP113, its eccentric, 4,300-year orbit has a perihelion of 80 AU and an aphelion—its farthest retreat from the sun—of 446 AU. Like Sedna, 2012 VP113 is fully detached from Neptune gravitationally. And crucially, its argument of perihelion is very similar to Sedna's, as well as to that of a handful of other, less Sedna-like KBOs. It was that last factor that led to a provocative line buried well down in the *Nature* paper. "This suggests," Trujillo and Sheppard wrote, "that a massive outer Solar system perturber may exist." The perturber, they hypothesized, could be a super Earth orbiting up to 250 AU from the sun, whose gravity might have influenced the smaller objects and synchronized their arguments of perihelion. "I don't think anyone was really thinking seriously about a massive, undetected planet before this," says Meg Schwamb of Yale University. "But the Trujillo and Sheppard paper really brought it into play."

Then, in September 2014, a paper in *Monthly Notices of the Royal Astronomical Society Letters* by two relatively obscure Spanish astronomers, brothers Raúl and Carlos de la Fuente Marcos of the Complutense University of Madrid, upped the ante. Based on the orbits of Sedna, 2012 VP113 and smaller bodies, they argued that there might not be just one super Earth. Their analysis "strongly suggest[ed]" that at least two planets might exist beyond Pluto. "Our unpublished calculations," Raúl says, "suggest that the hypothetical planets should be at least two, but probably fewer than 15, Earth masses."

Like Sheppard and Trujillo, the de la Fuente Marcos brothers do not claim to be making a solid prediction. Both teams say only that the existence of a super Earth is plausible. If it exists, however, astronomers' confidence that they fully understand our own solar system will be upended.

DOUBTS REMAIN

ALTHOUGH A HIDDEN PLANET X is a tempting explanation for the oddities of Sedna and its ilk, it is not the only option. Another possibility, says planet-formation theorist Hal Levison of the Southwest Research Institute is that Sedna, 2012 VP113 and the rest were thrown into their distinctive orbits while the sun was still part of its original birth cluster of thousands of stars that congealed from a single gas cloud. Before the cluster drifted apart, those stars would have been nearby enough to distort the orbits of objects in the outer solar system, sending them inward on long, stretched-out trajectories. Or, Sheppard says, the orbital elongations could have come from galactic tides—that is, a stronger pull from one direction than from another as the sun passes close to higher-density regions on its orbit around the center of the Milky Way. "We've run some simulations like that," Sheppard says, "and nothing has shown up. So it doesn't appear that that's likely, but there are a lot of other possibilities kind of like that out there."

Any of these effects could have put the objects on their oblong orbits, but only the super-Earth hypothesis could give them such closely matching arguments of perihelion. That or pure chance. The 12 objects Sheppard and Trujillo cite in their paper may sound like a lot, but given that there are millions of Kuiper belt objects, Sheppard says, "that's a statistically marginal number."

The case for Planet X from the odd orbits of Sedna and its fellows gets even more marginal if you agree with Schwamb and her collaborator Ramon Brasser of the Tokyo Institute of Technology. "Work we've done recently," Schwamb says, "shows there are really only four objects like Sedna." The rest of the 12 do not come all that close to Neptune, she says, but they come close enough that they could be feeling its gravity. Neptune itself could therefore be the Planet X that explains their closely matching arguments of perihelion. And if 12 objects are considered statistically marginal, four is even more so—although "marginal" in science means something slightly different than it does in the everyday world. "The alignment of the four remaining objects," Brasser says, "would happen by chance only 1 percent of the time." Long odds, however, are not a slam dunk. "Just because you can say a planet is possible," Schwamb says—which she agrees it is—"doesn't rule it in."

Planetary scientists have learned that lesson more than once. In the 1980s University of California, Berkeley, physicist Richard Muller thought he could explain many past mass extinctions of species on Earth by invoking a dim star or a brown dwarf—an object less massive than a star but more massive than a planet—orbiting the sun at a distance of roughly 100,000 AU, or about 1.5 light-years. Once every 26 million years, more or less, goes the theory, the object he called Nemesis kicks a knot of comets out of the Oort cloud, a still hypothetical shell of icy bodies that surrounds the solar system far beyond Sedna or anything else astronomers have ever seen. The Oort comets fall in toward the

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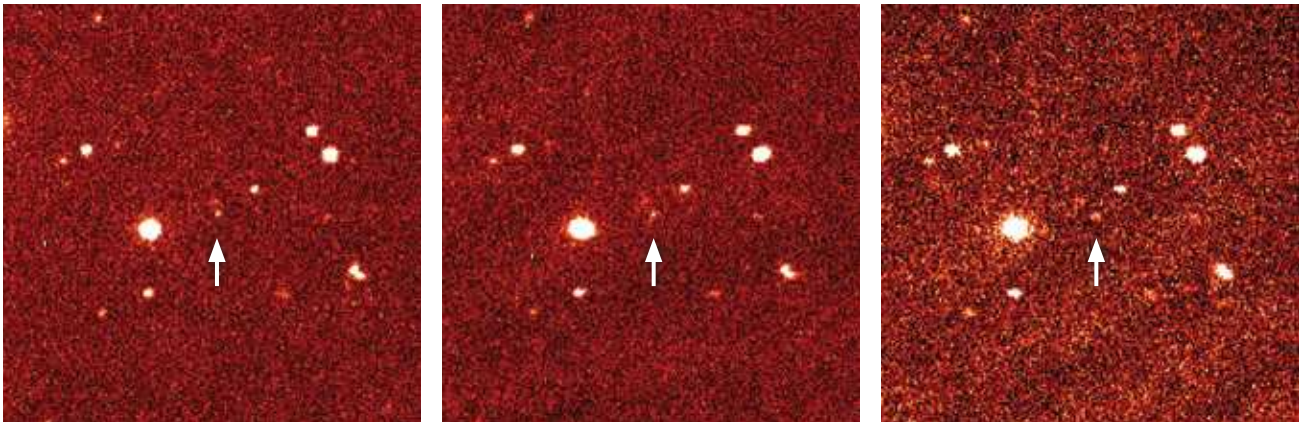

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THREE IMAGES taken roughly an hour and a half apart at Palomar Observatory in California show the movement of a faint object astronomers dubbed Sedna. The odd orbits of Sedna and similar bodies suggest there might be a hidden planet far beyond Pluto.

sun. Some of them slam into Earth, and there goes a large fraction of the species on our planet.

But just like today's arguments for Planet X, the theory was only barely plausible, and searches for Nemesis have consistently turned up empty. More recently, John Matese and Daniel Whitmire, while at the University of Louisiana at Lafayette, postulated a Jupiter-size planet in the far outer solar system to explain what seemed to be an excess of long-period comets coming in from one direction in the sky. "It was," Schwamb says, "a paper in the literature," which is scientific shorthand for "I never bought it in the first place." Sure enough, a sensitive survey by NASA's Wide-field Infrared Survey Explorer (WISE) telescope saw nothing. "We would have been able to see an object as small as Jupiter out to about maybe 30,000 to 40,000 AU from the sun," says Kevin Luhman of Pennsylvania State University, who conducted the search, "and we would have been able to see an object as small as Saturn out to maybe 10,000 or 15,000 AU from the sun." They found nothing. A super-Earth-size Planet X would be much closer but also so much dimmer that it would not have shown up in this survey.

SO IS IT THERE OR NOT?

WITH NO MORE than 12 unusual objects to guide them, planetary scientists cannot say at this point whether our solar system is host to a super Earth or not. They can say only that the hypothesis is consistent with the observations. Identifying more objects with similar orbital characteristics is crucial, which is why astronomers are so excited about a new object announced in November 2015. Known as V774104, it has a perihelion even farther from the sun than Sedna's. It is too early to know whether its orbit confirms or rejects the possibility of an undiscovered giant planet, says Sheppard, who led the discovery team. It is also too early to say much about the 40 or so other distant objects Sheppard's team found at the same time in what he calls "the deepest, widest survey of the outer solar system ever conducted." But the more the researchers find, the better their chances of saying definitively whether something massive lurks out there.

To improve their chances even more, planetary scientists are eager to get their hands on the Large Synoptic Survey Telescope (LSST), scheduled to come online in northern Chile by 2019. It will not be any bigger than the largest telescopes currently in use, but its field of view will be much wider, allowing it to search much broader swaths of sky. At present, Trujillo says, astronomers have surveyed about 10 square degrees of sky—the full moon, for comparison, covers a quarter of a square degree—in search of faint, distant objects. The LSST, he says, "will be able to survey tens of thousands."

If a super Earth is out there and if it is large and bright enough, the LSST could find it. Or perhaps someone else already has. In December 2015 observers claimed they had taken direct images of what could be a different super Earth using the Atacama Large Millimeter/submillimeter Array in Chile. Most of their colleagues were highly skeptical, but more observations could change that. Or perhaps some other telescope has inadvertently imaged our local super Earth. "Maybe it's sitting around on somebody's hard drive, and they just never noticed it because they weren't looking for it, or they weren't looking in the right way," Trujillo says. "People tend to see only what they're looking for." SA

Editor's note: *Even as this story was first being published in our February issue, Caltech astronomers Mike Brown and Konstantin Batygin announced even stronger evidence that Planet X is orbiting in the darkness out beyond Pluto—and they narrowed down the part of the sky where astronomers should look. Targeted searches for this unseen world are now under way.*

Michael D. Lemonick is author of *Mirror Earth: The Search for Our Planet's Twin* (Walker Books, 2012). For 21 years he was a science writer for *Time* magazine. He is now *Scientific American*'s opinion editor.

MORE TO EXPLORE

A Sedna-like Body with a Perihelion of 80 Astronomical Units. Chadwick A. Trujillo and Scott S. Sheppard in *Nature*, Vol. 507, pages 471–474; March 27, 2014.

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FROM OUR ARCHIVES

Planet X. Henry Norris Russell; July 1930.

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STREAMS OF GALAXIES flowing through space reveal the contours of a structure known as Laniakea, which contains our own Milky Way as well as 100,000 other large galaxies.

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ASTRONOMY

Our Place in the Cosmos

The Milky Way turns out to be part of a massive supercluster of galaxies that forms one of the largest known structures in the universe. This discovery is only the beginning of a new effort to map the cosmos

By Noam I. Libeskind and R. Brent Tully

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IMAGINE VISITING A FAR DISTANT GALAXY AND ADDRESSING A POSTCARD TO YOUR LOVED ONES BACK home. You might begin with your house on your street in your hometown, somewhere on Earth, the third planet from our sun. From there the address could list the sun's location in the Orion Spur, a segment of a spiral arm in the Milky Way's suburbs, followed by the Milky Way's residence in the Local Group, a gathering of more than 50 nearby galaxies spanning some seven million light-years of space. The Local Group in turn exists at the outskirts of the Virgo Cluster, a 50-million-light-year-distant cluster of more than 1,000 galaxies that is itself a small part of the Local Supercluster, a collection of hundreds of galaxy groups sprawled across more than 100 million light-years. Such superclusters are believed to be the biggest components of the universe's largest-scale structures, forming great filaments and sheets of galaxies surrounding voids where scarcely any galaxies exist at all.

Until recently, the Local Supercluster would have marked the end of your cosmic address. Beyond this scale, it was thought, further directions would become meaningless as the boundary between the crisp, supercluster-laced structure of galactic sheets and voids gave way to a homogeneous realm of the universe with no larger discernible features. But in 2014 one of us (Tully) led a team that discovered we are part of a structure so immense that it shattered this view. The Local Supercluster, it turns out, is but one lobe of a much larger supercluster, a collection of 100,000 large galaxies stretching across 400 million light-years. The team that discovered this gargantuan supercluster named it Laniakea—Hawaiian for "immeasurable heaven"—in honor of the early Polynesians who navigated the great expanse of the Pacific Ocean by the stars. The Milky Way sits far from Laniakea's center, in its outermost hinterlands.

Laniakea is more than just a new line on our cosmic address. By studying the architecture and dynamics of this immense structure, we can learn more about the universe's past and future. Charting its constituent galaxies and how they behave can help us better understand how galaxies form and grow while telling us more about the nature of dark matter—the invisible substance that astronomers believe accounts for about 80 percent of the stuff in the universe.

Laniakea could also help demystify dark energy, a powerful force only discovered in 1998 that is somehow driving the accelerating expansion of the universe and thus shaping the cosmos's ultimate fate. And the supercluster may not actually be the final line of our cosmic address—it could, in fact, be part of an even bigger structure yet to be discovered.

PROBING MYSTERIES WITH GALACTIC FLOWS

THE TEAM that discovered Laniakea did not exactly set out to find it. Instead Laniakea emerged from efforts to answer lingering fundamental questions about the nature of the universe.

Scientists have known for nearly a century that the cosmos is expanding, pulling galaxies away from one another like dots moving apart on the surface of an inflating balloon. Yet in recent decades it has become clear that most galaxies are not separating as fast as would be expected if expansion were the only force acting on them. Another, more local force is at work, too—the gravitational tugs from other nearby accumulations of matter, which can offset a galaxy's flow in the expansion of the cosmos. The difference between a galaxy's motion from cosmic expansion and the motion from its local environment is called peculiar velocity.

If we take all the stars in all the galaxies that we see and add all the gas and other ordinary matter that we know about, we fall short of explaining the gravitational sources of observed peculiar velocities by an order of magnitude. In our ignorance we astronomers call what is missing "dark matter." We presume this dark matter consists of particles that interact almost exclusively with the rest of the universe through gravity rather than through other forces such as electromagnetism and that the dark matter exerts the "missing" gravitational force needed to account for the observed velocities. Scientists think that galaxies sit within deep pools of dark matter—dark matter being the invisible scaffolding around which galaxies coalesce.

Tully's group and others realized that creating maps of galactic flows and peculiar velocities could reveal dark matter's hidden cosmic distribution, uncovering the mysterious substance's great-

IN BRIEF

Similar to how stars clump together into star clusters and galaxies, galaxies themselves gather into clusters, and galactic clusters group into superclusters.

These galactic superclusters are the building blocks of great filaments, sheets and voids that constitute the largest measurable structures in the universe.

Recent studies of the motions of thousands of nearby galaxies have revealed that the Milky Way's home supercluster is far larger than previously thought. Astronomers call this newfound supersized supercluster "Laniakea."

More detailed mapping of Laniakea and its neighboring superclusters could reveal new details about galaxy formation and help researchers solve the dual cosmological mysteries of dark matter and dark energy.

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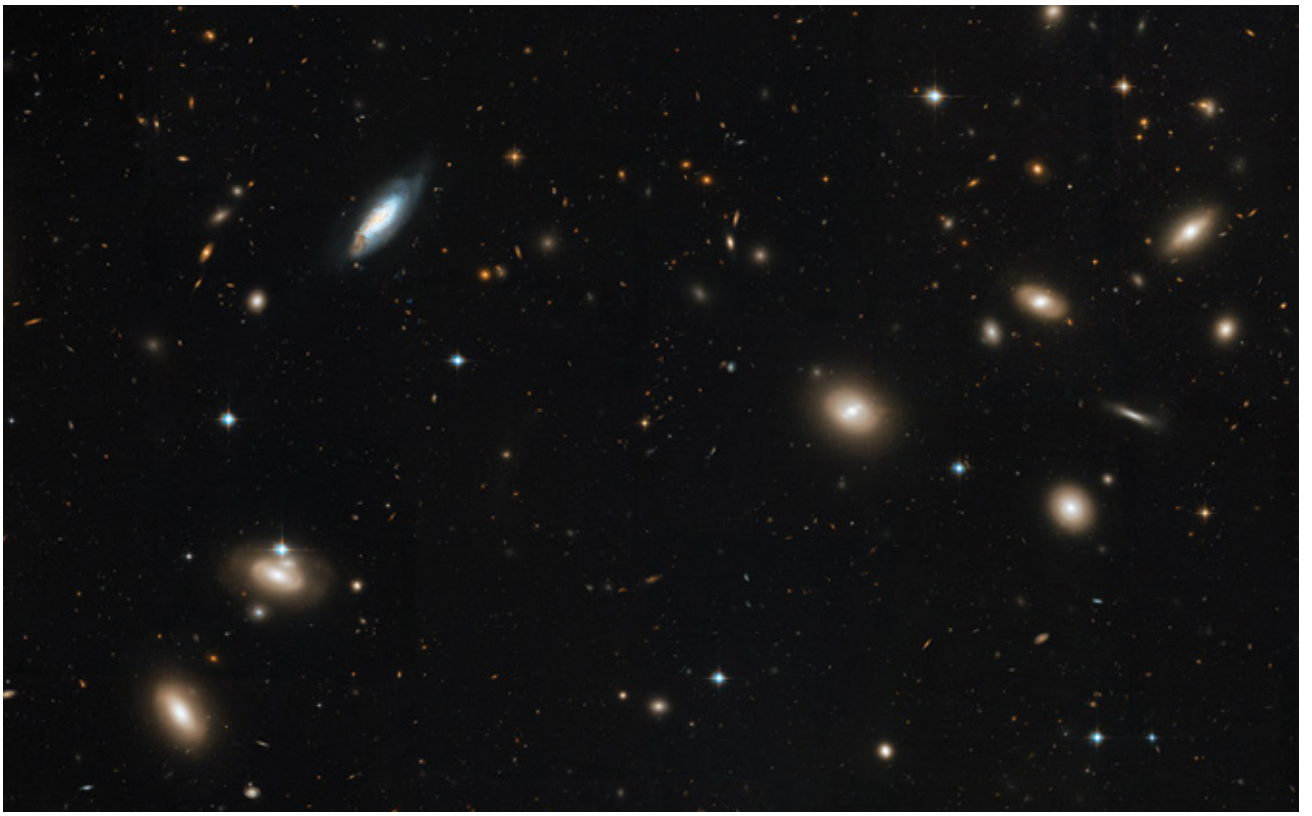

GALAXY CLUSTERS such as this one, the Coma Cluster, are building blocks for the largest structures in the universe. Located more than 300 million light-years away and containing about 1,000 large galaxies, the Coma Cluster is part of an even bigger structure—the Coma Supercluster—which lies beyond Laniakea's boundaries.

COURTESY OF NASA, ESA AND HUBBLE HERITAGE TEAM STScI/AURA

est concentrations by their gravitational influence on galaxies' motions. If, say, streams of galaxies are all flowing toward a particular point, one can assume that the galaxies are being gravitationally drawn to that point by a highly dense region of matter.

They also realized that pinning down the density and distribution of all forms of matter in the universe could help solve another, even deeper mystery: the fact that the cosmos is not only expanding but is doing so at an accelerating rate. This behavior is as counterintuitive as a rock tossed up in the air rushing onward into the heavens rather than falling back to Earth. Whatever powers this bizarre phenomenon is dubbed "dark energy" and has profound implications for the future of the universe. The accelerated expansion suggests the cosmos will ultimately experience a cold death, with most galaxies racing away from one another at accelerating speeds until a final darkness descends on the universe as every star in every galaxy dies and all matter cools to absolute zero. But knowing for sure how it all will end requires not only determining what exactly dark energy is but also how much matter is in the universe: Given a sufficiently high density of matter, in the far future our universe could reverse its expansion to collapse in on itself as a consequence of the self-gravity of its cumulative mass. Or it could instead possess a balanced density of matter that would lead to an infinite but ever slowing expansion.

It was this charting of galactic flows to map the cosmic density of ordinary and dark matter that ultimately led to the unveiling of Laniakea.

FINDING LANIAKEA

MAPPING GALACTIC FLOWS requires knowing both a galaxy's motion stemming from cosmic expansion and its motion stemming from nearby matter. As a first step, astronomers measure a galaxy's redshift—the stretching out of the galaxy's emitted light as it recedes away from us through the expanding universe. A whistle or siren moving toward us has a higher pitch than if moving away because its sound waves are compressed to higher frequencies and shorter wavelengths. Similarly, light waves from a galaxy moving away from us are shifted to lower frequencies and longer, redder wavelengths—the faster they are receding, the more redshifted they become. Thus, a galaxy's redshift gives astronomers a measure of its overall velocity and a rough estimate of its distance.

Astronomers can infer how much of a galaxy's velocity is the result of local gravitational tugging by measuring its distance through other techniques besides redshift. For instance, based on rigorous estimates of the universe's expansion rate, a galaxy measured to be 3.25 million light-years away should have a velocity of about 70 kilometers per second. If instead the galaxy's redshift yields a velocity of 60 kilometers per second, astronomers could infer that matter concentrations near that galaxy are giving it a peculiar velocity of 10 kilometers per second. The techniques used to provide redshift-independent distance measurements mostly rely on the fact that light's intensity decreases by the inverse square of the distance from its source. That is, if you see two identical lighthouses but one appears a quarter as

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YOU ARE HERE

Cosmic Landscape

Although they contain hundreds of billions of stars, galaxies are not the largest structures in the universe. Bound together by gravity, hundreds of galaxies can group together as a galaxy cluster. Gravity can concentrate galaxy clusters together, too, forming superclusters composed of hundreds of thousands of galaxies. In this hierarchy, our solar system's cosmic address has traditionally been: the Milky Way galaxy, the Local Group, the Virgo Cluster and, finally, the Local Supercluster. Now, however, new research is revealing that our Local Supercluster is only part of another supercluster more than 100 times larger. This larger supercluster is Laniakea, which in Hawaiian means "immeasurable heaven."

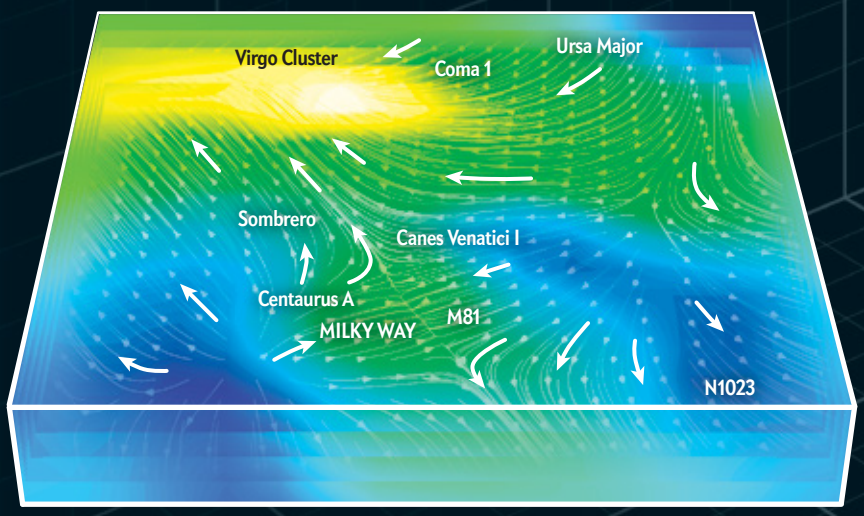
MAPPING THE LANIAKEA SUPERCLUSTER

Considered collectively, the positions and motions of galaxies can either diverge as the universe expands or converge in response to gravity. Supercluster boundaries can be drawn wherever the convergent force of gravity begins to significantly impede the expansion-caused divergent motion of galaxies. Here the positions of more than 8,000 galaxies are mapped and colored according to their relative motions (their velocity and trajectory when both convergent and divergent motion are taken into account). Contours with warmer colors (*yellows* and *pinks*) represent galaxy clusters rapidly converging together. Laniakea's outline appears in cooler blue, delineating where clusters are converging at their slowest. Spanning nearly half a billion light-years, Laniakea encompasses a volume of galaxy clusters that, in the absence of cosmic expansion, would converge to become a single gravitationally bound structure. Beyond Laniakea's boundaries, Shapley, Hercules, Perseus-Pisces and other neighboring superclusters can be seen.

LANIAKEA

GOING WITH THE FLOW

Zooming in on Laniakea's finer details can yield new insights into the distribution of dark matter and the process of galactic evolution. For instance, consider a three-dimensional slice of Laniakea containing the Milky Way and its enclosing Local Group of galaxies (*detail below*). The arrows track the motions of galaxies, which flow like water toward areas where matter is dense and gravity is strong (*depicted in warmer colors*) and away from regions of low density (*cooler colors*). The bulk flows of galaxies reveal cosmic concentrations of matter (be it normal or dark). Flow measurements by Libeskind have shown that the Local Group is falling along a 50-million-light-year-long filament of dark matter toward the Virgo Cluster (*yellow*), a gathering of more than 1,000 galaxies squeezed into a volume of 13 million light-years. Such filaments are thought to play important roles in the formation and evolution of galaxies.



SOURCES: "PLANES OF SATELLITE GALAXIES AND THE COSMIC WEB," BY NOAM I. LIBESKIND ET AL., IN *MONTHLY NOTICES OF THE ROYAL ASTRONOMICAL SOCIETY*, VOL. 452, NO. 1; SEPTEMBER 1, 2015 (*inset slab*); DANIEL POMARÈDE, HÉLÈNE M. COURTOIS, YEHUDA HOFFMAN AND BRENT TULLY (*data for Laniakea illustration*)

TOP SCIENCE STORIES OF 2016

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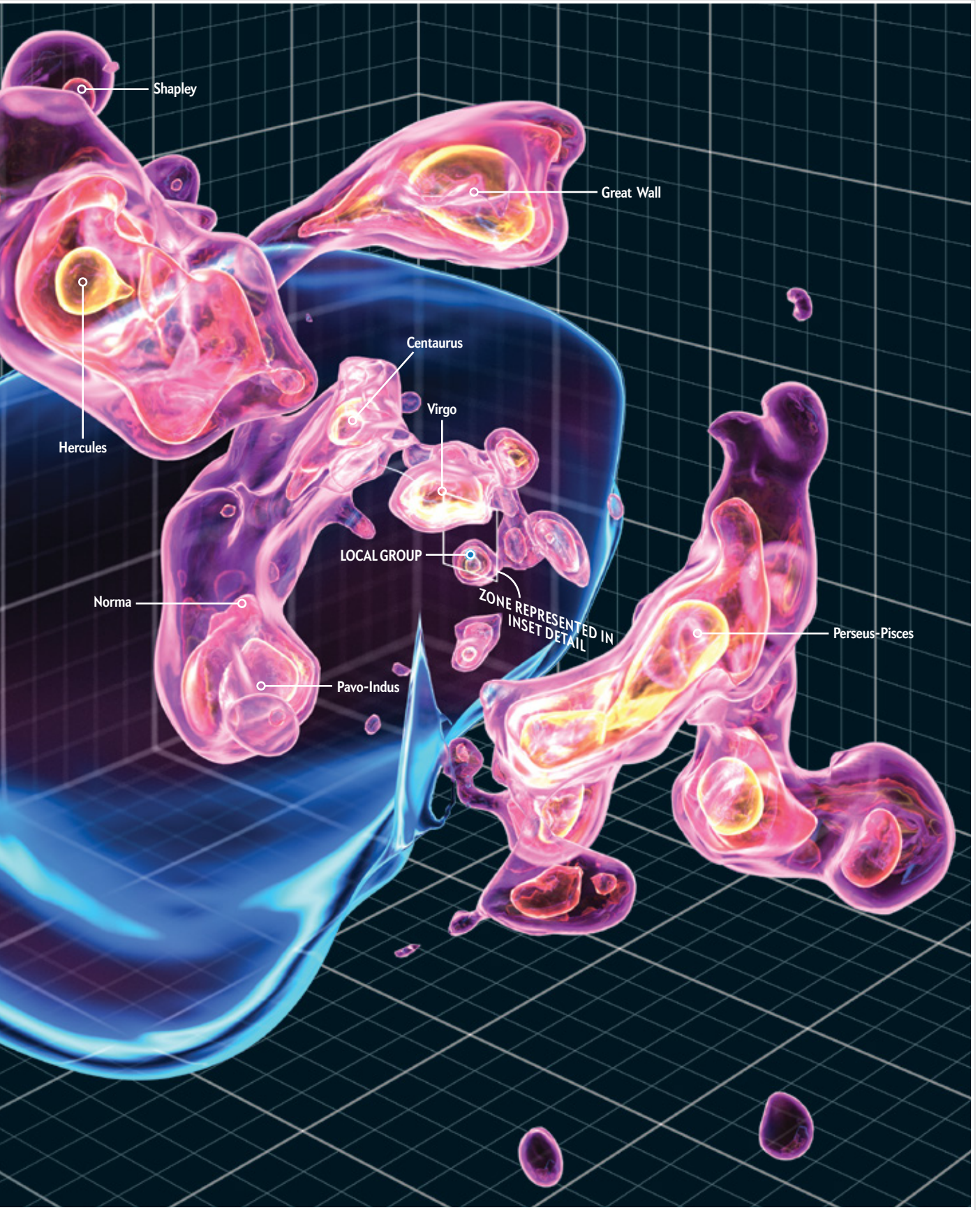

Illustration by Bryan Christie

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bright, then you know the fainter one is two times farther away. In astronomy, such identical lighthouses are called standard candles, astrophysical objects that always shine with the same brightness no matter where they are in the universe. Examples include certain types of exploding or pulsating stars—or even massive galaxies as first proposed by Tully and astronomer J. Richard Fisher in 1977. This Tully-Fisher relation draws on the fact that massive galaxies are both more luminous and rapidly rotating than small galaxies—they have more stars and must spin faster to maintain stability in their stronger gravitational fields. Measure the galaxy's rotation rate, and you learn its intrinsic luminosity; compare that with its apparent luminosity, and you learn its distance.

Each distinct standard candle has a different range where it works best. The pulsating stars called Cepheid variables can only be well observed if the galaxies are close to the Milky Way, and so they are unsuitable for large-scale distance measurements. The Tully-Fisher relation can be used with many spiral galaxies, but the distance estimates they yield have uncertainties of up to 20 percent. Exploding stars called type Ia supernovae yield measurements with half as much uncertainty and shine across vast cosmic distances, but they are rare, only occurring once a century in a good-size galaxy.

If peculiar velocities for a large sample of galaxies in the universe can be obtained, astronomers can then map the largest-scale galactic flows. On these immense scales, the flow of galaxies can be compared with rivers winding through what we call cosmic watersheds, with motions defined by gravitational forces from nearby structures rather than topography. In these "cosmographic" maps, galaxies flow in currents, swirl in eddies and collect in pools to indirectly reveal the structure, dynamics, origins and futures of the largest accumulations of matter in the universe [*see box on two preceding pages*].

GALAXIES FLOW IN CURRENTS, SWIRL IN EDDIES AND COLLECT IN POOLS TO REVEAL THE STRUCTURE, DYNAMICS, ORIGINS AND FUTURES OF THE LARGEST ACCUMULATIONS OF MATTER IN THE UNIVERSE.

Mapping on the scale needed to address our questions about dark matter and dark energy required cataloguing all the best available data from a large number of observational programs. In 2008 Tully, Hélène M. Courtois, now at the Institute of Nuclear Physics of Lyon in France, and their colleagues published the Cosmicflows catalog, which collated multiple data sets to detail the dynamics of 1,800 galaxies within 130 million light-years of the Milky Way. The team expanded its efforts in 2013 with the Cosmicflows-2 catalog, mapping the motions of about 8,000 galaxies within a volume of about 650 million light-years. One member of the team, Yehuda Hoffman of the Hebrew University of Jerusalem, developed methods to precisely derive the distribution of dark matter from the peculiar velocities of the Cosmicflows data.

As the catalog expanded, we were amazed to find an unexpected pattern hidden in the mass of data: the outlines of a new, previously unseen cosmic structure. Clusters of galaxies across a span of more than 400 million light-years all moved together within a local "basin of attraction," akin to water pooling at the lowest point of a landscape's topography. Were it not for the universe's incessant expansion, these galaxies would eventually coalesce into one compact, gravitationally bound structure. All together, this vast swarm of galaxies constituted the Laniakea supercluster.

So far studies of the motions of Laniakea's galaxies show them behaving exactly as would be expected from leading models of dark matter's cosmic distribution—although we cannot see it, we can predict with reasonable accuracy where the universe's invisible stuff accumulates. Furthermore, for better or worse, the total density of visible and dark matter within Laniakea suggests that, just as dark energy theorists thought, the universe is destined for a cold death of ever accelerating expansion.

These conclusions remain provisional. The daunting task of mapping galactic flows still has a long way to go. Currently only 20 percent of galaxies within 400 million light-years also have peculiar velocity determinations, and many standard-candle distance measurements still have large uncertainties. Even so, the emerging map of our galactic neighborhood is giving us a new appreciation of our perch in the cosmographic basins and ranges of the universe.

OUR COSMOGRAPHIC CONTEXT

LET'S TAKE A TOUR of the flowing, rushing components of our newly discovered home, Laniakea, starting with its most familiar part—you. No matter how slow or fast you are traveling on Earth as you read this, you are spinning around the sun, along with the rest of our planet, at about 30 kilometers per second. The sun in turn orbits the galactic center at roughly 200 kilometers per second, and the entire Local Group, including the Milky Way, is hurtling toward a mysterious concentration of mass in the direction of Centaurus at more than 600 kilometers per second (more on this later). You probably never realized you could move so fast simply by reading a magazine article—or doing nothing at all.

Zooming out from the Milky Way, our journey through Laniakea's expanse begins with two dwarf galaxies, the Small and Large Magellanic Clouds a "mere" 180,000 to 220,000 light-years away. You can glimpse the Magellanics from Earth's Southern Hemisphere, but for the best views you must travel all the way to Antarctica, during the winter. The only other galaxy visible with the naked eye is the giant spiral of Andromeda, although it appears just as a fuzzy patch in a very dark sky.

Andromeda is two and a half million light-years away and is speeding toward us at a peculiar velocity of some 110 kilometers per second. In roughly four billion years it will slam into the Milky Way in a head-on collision and transform both galaxies into a single, featureless ellipsoid of old red stars. It is unlikely that our solar system will be affected during this cosmic car crash—the distance between stars is so large that no two stars are likely to get close enough to collide. The Milky Way, Andromeda and four dozen other galaxies are members of the Local Group, a region where gravity has won the battle against cosmic expansion and is undergoing collapse. Like the Milky Way itself, with its Magellanic Clouds, all these large galaxies have their own entourages of dwarfs.

Just beyond the Local Group, within a volume of about 25 mil-

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lion light-years, three distinctive features appear in our maps. Most of the galaxies here, including our own, live in the unimaginatively named Local Sheet. As "sheet" would imply, it is very thin—most of its galaxies are within three million light-years of this structure, itself the equatorial plane of what is referred to as the supergalactic coordinate system. Below this plane, after a gap, is a filament of galaxies—the Leo Spur—as well as galaxies in the so-called Antlia and Doradus Clouds. Above the plane there is mostly nothing nearby. This emptiness is the domain of the Local Void.

If only the galaxies within the Local Sheet are considered, the situation seems very tranquil. These galaxies are flying apart at the rate of the cosmic expansion, with only small peculiar velocities caused by local interactions. Below the Local Sheet, the galaxies of the Antlia and Doradus Clouds and the Leo Spur have small peculiar velocities, too. They are, however, approaching the Local Sheet at high speed. The Local Void is the probable culprit. Voids expand like inflating balloons, and matter moves from underdense to overdense regions to pile up at their boundaries. We now appreciate that the Local Sheet is a wall of the Local Void and that this void is expanding to push us down toward Antlia, Doradus and Leo.

Zooming farther out, we encounter the Virgo Cluster, which is 300 Local Groups' worth of galaxies squeezed into a volume with a diameter of 13 million light-years. These galaxies whiz around at typical speeds of 700 kilometers per second, and any galaxies within 25 million light-years of the cluster's exterior are falling inward to become part of it within 10 billion years. The full extent of Virgo's domain, the region it will eventually capture, extends to a current radius of 35 million light-years. Interestingly, our Milky Way, at 50 million light-years distant, lies just outside this capture zone.

THE GREAT GALACTIC FLOW

THE GREATER REGION around the Virgo Cluster that extends to our location is called the Local Supercluster. Almost 30 years ago a group of astronomers who became identified by the convivial moniker "the Seven Samurai" discovered that it is not just the Milky Way moving hundreds of kilometers per second in the direction of Centaurus but rather the entire Local Supercluster. They called the mysterious mass pulling all these galaxies together the Great Attractor. In many ways, the Great Attractor is not so mysterious—the density of matter in that direction of the cosmos is obviously high because it contains seven clusters comparable to the Virgo Cluster lying within a sphere 100 million light-years wide. Three of the largest clusters are called Norma, Centaurus and Hydra.

According to our conception of superclusters as cosmic watersheds, which draws their boundaries based on the divergent movements of galaxies, the so-called Local Supercluster is misnamed. It is only part of something bigger—namely, Laniakea, which encompasses other large structures such as the Pavo-Indus filament and the Ophiuchus Cluster. Imagining Laniakea as a city, our traffic-heavy downtown would be the Great Attractor region. As with most urban cores, it is hard to specify a precise center, but an approximation would place it somewhere between the Norma and Centaurus clusters. This positioning puts our Milky Way far out in the suburbs, near the borders of an adjacent supercluster called Perseus-Pisces. This border is so relatively close in cosmic terms that we can study it in detail to define Laniakea's blobby, roughly round, half-billion-light-year-wide boundary. In total, Laniakea's boundaries encompass a mass from both normal and dark matter equivalent to some 100 million billion suns.

Astronomers have been glimpsing the outlines of what may lie beyond Laniakea for decades. Soon after the discovery of the Great Attractor by the Seven Samurai, something even larger emerged from the intergalactic murk. Directly behind the Great Attractor region, but three times farther away, is a monstrous accumulation of clusters—the densest known within the local universe. Because astronomer Harlow Shapley first spied evidence for its existence in the 1930s, this distant, huge structure became known as the Shapley Supercluster. (Incidentally, just like the Local Sheet, the Virgo Cluster and the main band of the Local Supercluster, as well as the Great Attractor and Shapley Supercluster, all lie on the supergalactic equator. Imagine an immense pancake of galactic superclusters, and you have a good picture of our large-scale local environs.)

So what is causing our Local Supercluster's peculiar velocity of 600 kilometers per second? To some degree, the culprit must be the Great Attractor complex. But we must also consider the gravitational pull of the Shapley Supercluster, which is three times farther away but bears four times the number of rich clusters. Now, according to the Cosmicflows-2 compendium—the same catalog that revealed Laniakea—there is even more to the story. The peculiar velocities of the 8,000 galaxies within this catalog demonstrate a coherent flow toward the Shapley Supercluster. This flow encompasses the entire volume of the Cosmicflows-2 catalog, 1.4 billion light-years from end to end. Does it stop there? We do not yet know. Only even bigger surveys mapping even larger swaths of the universe can reveal the ultimate source—and ultimate structure—behind the epic flow of galaxies in our local universe. SA

Noam I. Libeskind is a cosmologist at the Leibniz Institute for Astrophysics Potsdam in Germany. He uses supercomputers to model the evolution of the universe and the formation of galaxies, with a focus on the Milky Way, the Local Group and the small dwarf galaxies that surround us. Follow Libeskind's astrophysics tweets: @satellitegalaxy

R. Brent Tully is an astronomer at the University of Hawaii who, for 40 years, has been measuring the distances to galaxies and mapping their distribution and motions in space. His *Atlas of Nearby Galaxies*, co-written with J. Richard Fisher and published in 1987, is still the most extensive print atlas of the structure of our cosmic neighborhood. Tully takes pride in finding his way without recourse to GPS.

MORE TO EXPLORE

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COSMOLOGY

THE EMPTIEST PLACE IN SPACE

Efforts to explain a strange cold spot in the cosmos have led to the discovery of something even odder: ***a vast area with very little matter***

By István Szapudi

Illustration by Maria Corte Maidagan

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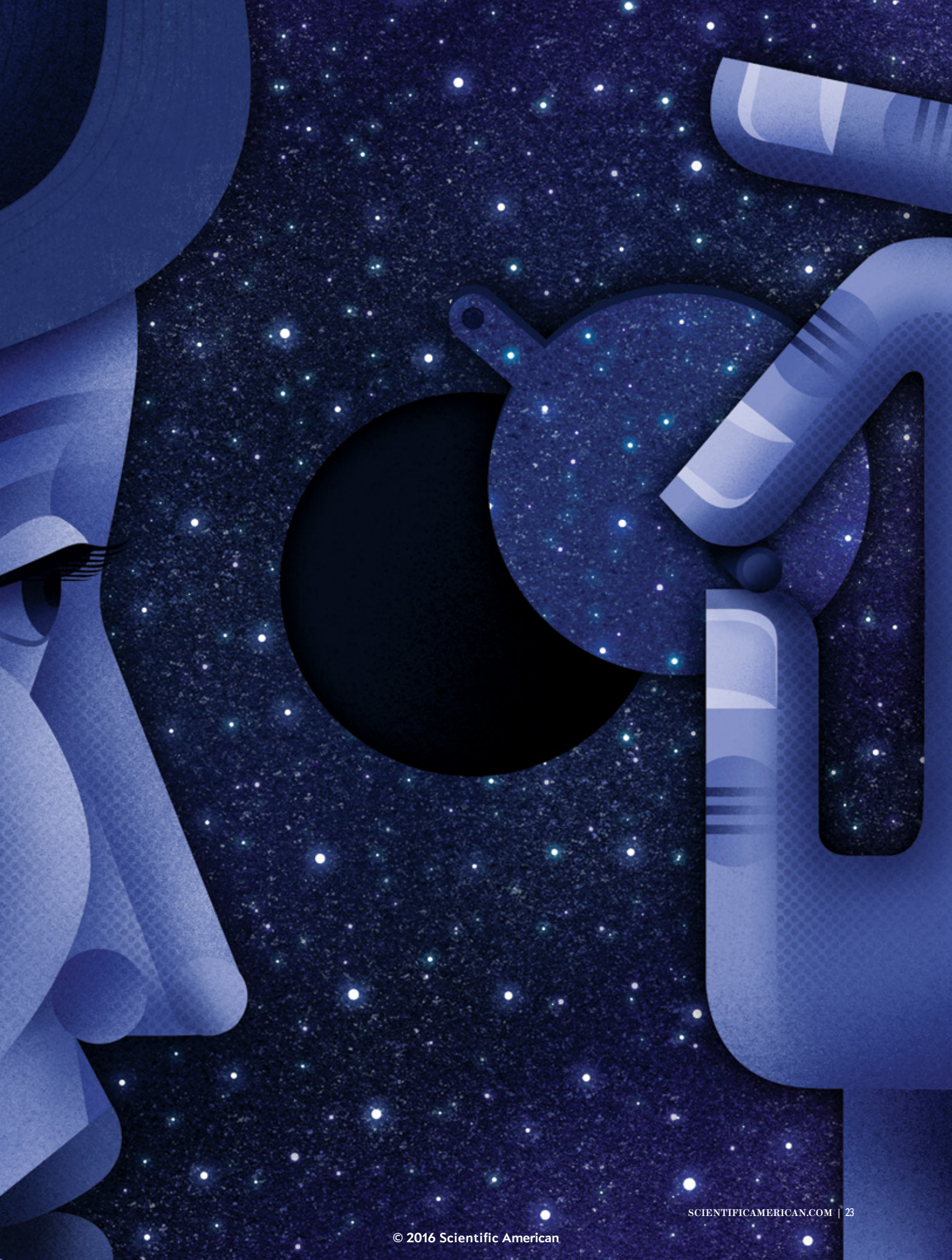

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TO GLIMPSE THE OLDEST LIGHT IN THE UNIVERSE, SIMPLY TUNE AN OLD TELEVISION between channels: some of the tiny specks dancing on the screen result from the antenna being bombarded relentlessly by photons that were emitted shortly after the big bang, some 13.8 billion years ago. These photons fly uniformly through space from all directions, with an average temperature of 2.7 kelvins (–455 degrees Fahrenheit), composing a cloud of radiation called the cosmic microwave background (CMB). Because these photons are so old, the familiar two-dimensional map of the CMB is often called a "baby picture" of the universe, providing a window back into the primordial conditions that created the cosmos we see around us today.

Our baby picture, however, has a few imperfections. Physicists like myself call them anomalies because they cannot be fully explained by our standard cosmological theories. The largest of these anomalies, first found in NASA's Wilkinson Microwave Anisotropy Probe (WMAP) map of the CMB in 2004, is the "cold spot," an area of the sky covering about 20 times the width of the full moon, where the ancient photons are unusually chilly. The cold spot is not unlike a beauty mark on our baby picture: for some, it is an ugly mole that breaks the majestic symmetry of the CMB; for others, it enhances the features of the universe and adds to the excitement. I am in the latter camp: I have always been fascinated with this CMB anomaly and what might account for it.

That puzzle has stimulated much discussion among scientists. One explanation might be that it arose by sheer chance, with no specific cause. But the odds of chance being the cause are low: about one in 200. Other possibilities range from the mundane to the fantastic—from problems with the instruments analyzing the cosmos to the suggestion that the cold region is a portal to another universe or hidden dimensions.

In 2007, by extrapolating from some known features of the cosmos, I and other astrophysicists hit on the idea that just such a cold spot might be expected to form if the cosmos contained a supervoid—a vast expanse of space relatively devoid of matter and galaxies—in the same region of the sky. This void would be the emptiest place in space, a rare gigantic wasteland amid relatively dense surroundings. The theory had enormous implications. If such a void did indeed exist and cause the cold spot in the way we imagined, the huge empty region might, for complex reasons, also provide proof for dark energy, the theorized culprit behind the accelerating expansion of the universe. Today my colleagues and I at the University of Hawaii have confirmed the void, and we are finding tantalizing clues that it could indeed account for the cold spot.

CROSSING THROUGH A VOID

SCIENTISTS CAME TO THE IDEA that a supervoid might exist and give rise to the cold spot by contemplating the way we think light interacts with smaller voids. The postulated supervoid would be extreme, but regular midsize voids—areas containing relatively few galaxies—are common in the universe. So are their opposites, clusters, which are large conglomerations of up to thousands of galaxies. Cosmologists think that the seeds of voids and clusters arose in the very early universe,

IN BRIEF

The cosmic microwave background (CMB), the ancient light that pervades the universe, shows an odd "cold spot" where its photons are significantly cooler than average.

One possible explanation is a theorized giant supervoid—a vast region of relatively empty space in the same region of the sky as the cold spot. Light traveling through a supervoid would tend to lose energy (become colder) because of what is called the integrated Sachs-Wolfe (ISW) effect produced by the accelerating expansion of the universe.

Astronomers have recently discovered a supervoid extending 1.8 billion light-years across aligned with the cold spot. They need to collect more data to determine for sure if it is responsible for the CMB's chilly zone.

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COURTESY OF ROB RATKOWSKI AND PS1 OBSERVATORY

SCANS OF THE SKY by the Panoramic Survey Telescope and Rapid Response System (Pan-STARRS) on Maui helped astronomers identify an immense expanse of relatively empty space—a "supervoid"—that may explain an enigmatic cold spot in the universe's oldest light.

when random quantum-mechanical processes caused matter to be slightly less dense in some parts of space and slightly more dense in others. The greater mass in the overdense regions wielded a stronger gravitational pull that drew more matter to them over time, pulling it away from the underdense locations. The former eventually grew into clusters, and the latter became voids.

Because voids have little matter, they act like hills on anything passing through them [*see box on page 27*]. As a particle moves into the void, away from the stronger gravitational pull of surrounding higher-density areas, it slows down like a ball rolling up a hill; once it starts to move out of the void toward the dense areas, it accelerates as if rolling down the hill. CMB photons behave similarly, although they do not change speed (the speed of light is always constant). Instead they change in energy, which is directly proportional to their temperature. As a photon enters a void, it climbs the hill and loses energy—that is, it cools down. Rolling down the hill on the other side, the photon regains its energy. Hence, it would arrive on the other side with the same temperature it started out with—if the universe were not expanding at an accelerating rate.

In the past two decades, though, scientists have discovered that the cosmos is not only expanding but that this expansion seems to be speeding up. Most cosmologists attribute the acceleration to dark energy, a putative kind of negative pressure throughout space that seems to be counteracting the inward pull of gravity. The acceleration of the universe adds a wrinkle to the hill scenario—from the perspective of our CMB photon, it means that while it crossed the void, the plain surrounding the hill effectively rose, so that the flat ground on the far side became higher than it was on the near side. As a result, the photon cannot regain all the energy it lost when it climbed the hill. The net effect is that CMB photons would lose energy when crossing a void. Consequently, we should see temperature dips on the microwave background near low-density regions. This phenomenon is called the integrated Sachs-Wolfe (ISW) effect. The effect also applies to superclusters, but in that case, photons would gain net energy when crossing vast areas with extra mass.

The ISW effect is expected to be tiny. Even for large voids, it would typically create temperature variations smaller than the average fluctuations in the CMB, which can vary by roughly one part in 10,000 because of slight differences in the density of the nascent universe when the light was released. But in the case of a truly huge void—a supervoid—the difference, we realized, might be enough to generate the cold spot. And if we could demonstrate that the supervoid existed and was the driving force behind the anomaly, we would do more than explain the cold spot. We would also offer a smoking gun for dark energy because the ISW effect can occur only if dark energy is operating on the universe, accelerating its expansion.

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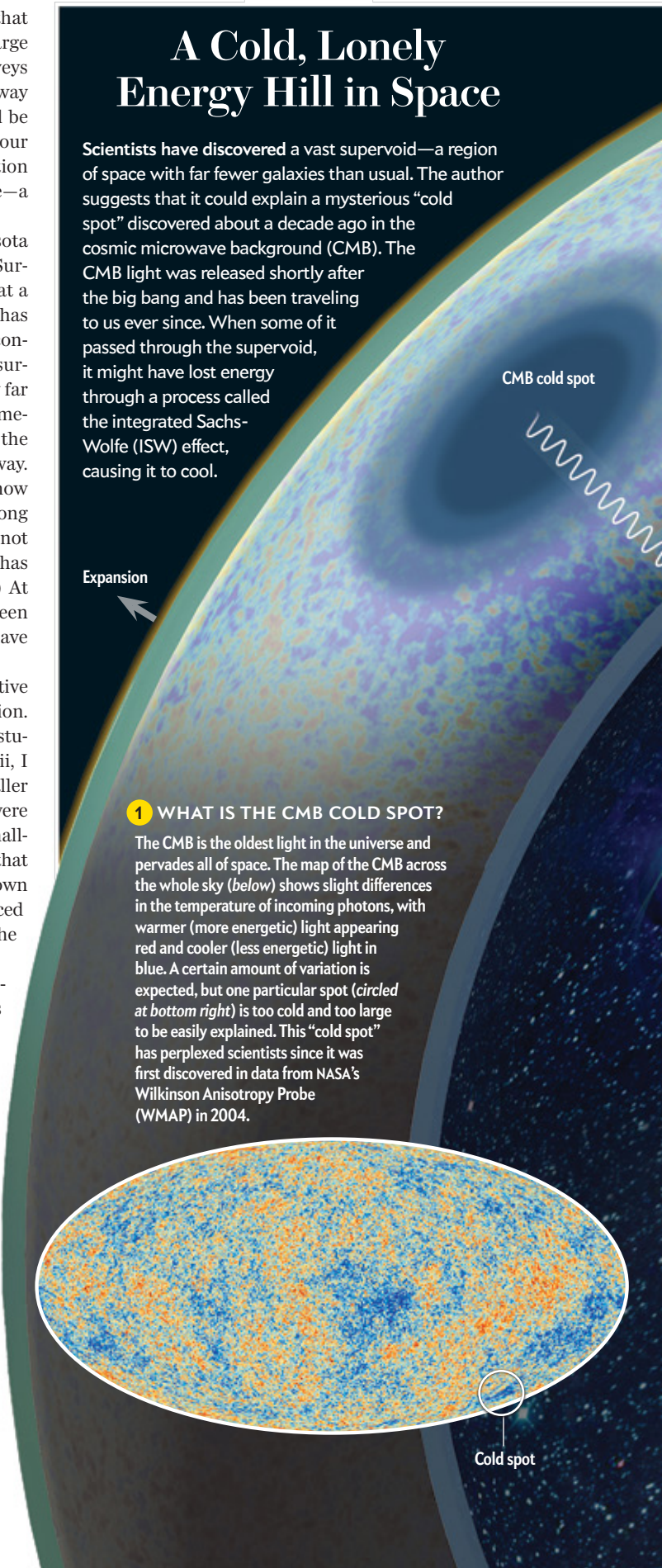
THEORY

A Cold, Lonely Energy Hill in Space

Scientists have discovered a vast supervoid—a region of space with far fewer galaxies than usual. The author suggests that it could explain a mysterious "cold spot" discovered about a decade ago in the cosmic microwave background (CMB). The CMB light was released shortly after the big bang and has been traveling to us ever since. When some of it passed through the supervoid, it might have lost energy through a process called the integrated Sachs-Wolfe (ISW) effect, causing it to cool.


CMB cold spot
Expansion
1 WHAT IS THE CMB COLD SPOT?
The CMB is the oldest light in the universe and pervades all of space. The map of the CMB across the whole sky (*below*) shows slight differences in the temperature of incoming photons, with warmer (more energetic) light appearing red and cooler (less energetic) light in blue. A certain amount of variation is expected, but one particular spot (*circled at bottom right*) is too cold and too large to be easily explained. This "cold spot" has perplexed scientists since it was first discovered in data from NASA's Wilkinson Anisotropy Probe (WMAP) in 2004.
Cold spot

COURTESY OF ESA AND PLANCK COLLABORATION (*CMB*)

THE HUNT FOR A SUPERVOID

ASTRONOMERS FIRST BEGAN looking for a supervoid that overlapped with the cold spot in 2007. Detecting such a large structure is harder than it sounds. Most astronomical surveys produce 2-D pictures of the sky without telling us how far away the objects in the pictures lie. The galaxies we see could all be clumped together, or they could be widely spaced out along our line of sight. Astronomers must gather further information about each galaxy individually to try to estimate its distance—a laborious and often prohibitively expensive task.

In 2007 Lawrence Rudnick of the University of Minnesota and his collaborators were looking at the NRAO VLA Sky Survey (NVSS) catalog of galaxies in radio waves and found that a region of space approximately aligned with the cold spot has fewer galaxies than average. Although the NVSS did not contain any data on the specific distances to the galaxies in the survey, the astronomers knew that most NVSS galaxies are very far from us. Based on the data, they hypothesized that an extremely vast supervoid that could produce the cold spot through the ISW effect might be present roughly 11 billion light-years away. One difficulty with this idea was that light reaching us now would have crossed through such a distant supervoid a long time ago—roughly eight billion years in the past. (It would not have been a full 11 billion years ago, because the universe has expanded to twice to its size since the light was emitted.) At such an early cosmic epoch, dark energy would not have been as strong a force as it is today, and so the ISW effect might have been too slight to yield the cold spot.

Rudnick's work, although it failed to turn up definitive evidence for a supervoid, nonetheless caught my attention. Along with Ben Granett and Mark Neyrinck, then a Ph.D. student and a postdoc, respectively, at the University of Hawaii, I conducted a statistical analysis to determine how often smaller features in the CMB—relatively warm or cool areas that were less extreme than the cold spot—appeared to overlap with smaller known clusters and voids in the universe, and we found that such overlaps were common. Even though none of these known structures could account for the cold spot, the results convinced us that the search for a supervoid that overlapped with the cold spot was not foolhardy and was worth continuing.

We then designed observations with the Canada-France-Hawaii telescope (CFHT) that targeted several small fields in the cold spot area and counted the number of galaxies in them. To our disappointment, when we made the observations in early 2010 we found no sign of a supervoid at the distance that Rudnick predicted. In fact, we could rule out the presence of a supervoid beyond distances of about three billion light-years. A similar search conducted by Malcolm Bremer of the University of Bristol in England and his collaborators yielded no results either.

At the same time, the statistical significance of the original paper by Rudnick was reevaluated by peers and turned out to be lower than thought. Thus, for a while it looked like we needed to give up on the ISW explanation for the cold spot.

There was a silver lining, however. We found a hint in our data that a supervoid might be lurking close to us. Paradoxically, finding one nearby is harder using the type of data we obtained with the CFHT: in the fields we ob-

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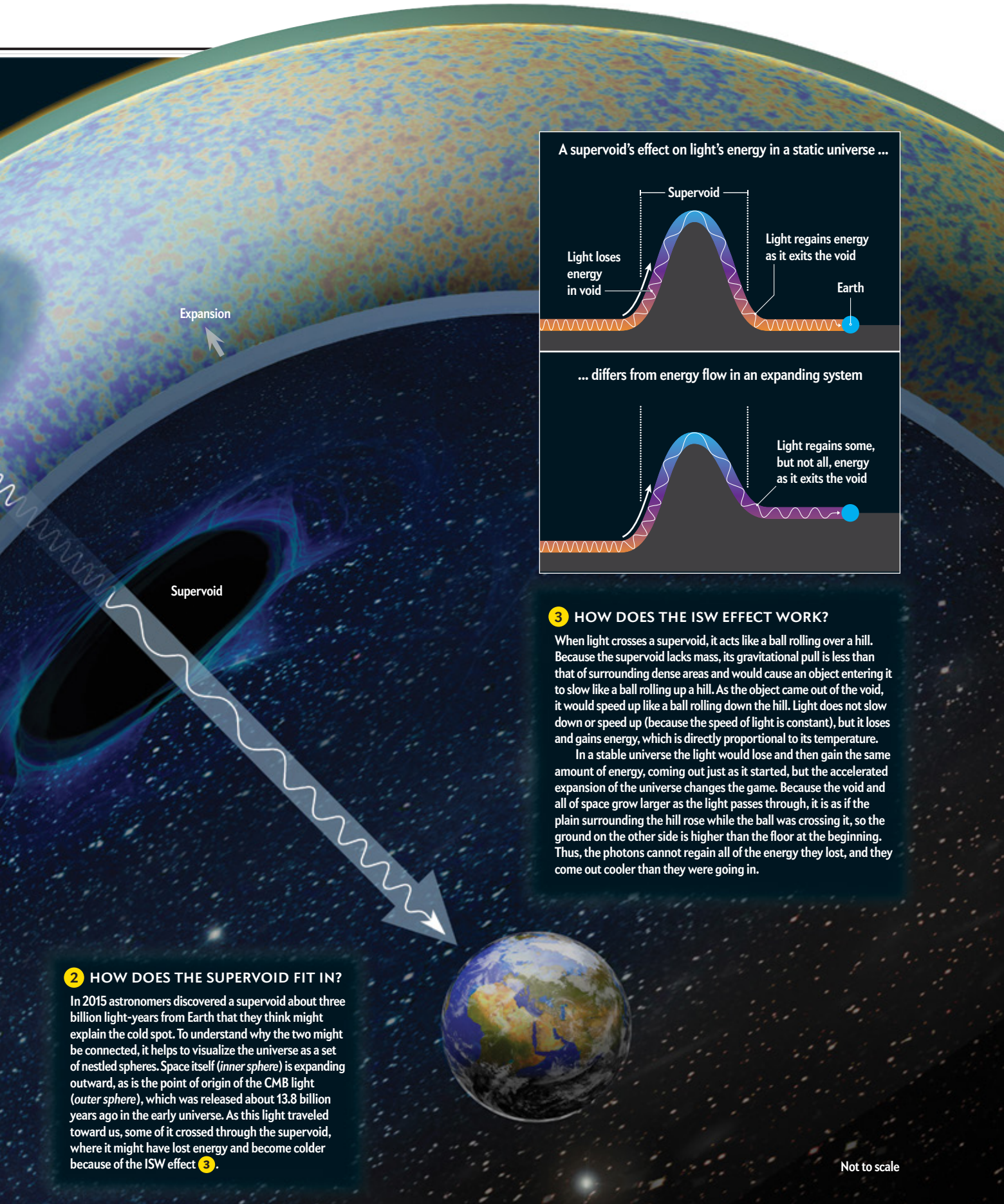

A supervoid's effect on light's energy in a static universe ...
Supervoid
Light loses energy in void
Light regains energy as it exits the void
Earth
... differs from energy flow in an expanding system
Light regains some, but not all, energy as it exits the void

3 HOW DOES THE ISW EFFECT WORK?

When light crosses a supervoid, it acts like a ball rolling over a hill. Because the supervoid lacks mass, its gravitational pull is less than that of surrounding dense areas and would cause an object entering it to slow like a ball rolling up a hill. As the object came out of the void, it would speed up like a ball rolling down the hill. Light does not slow down or speed up (because the speed of light is constant), but it loses and gains energy, which is directly proportional to its temperature.

In a stable universe the light would lose and then gain the same amount of energy, coming out just as it started, but the accelerated expansion of the universe changes the game. Because the void and all of space grow larger as the light passes through, it is as if the plain surrounding the hill rose while the ball was crossing it, so the ground on the other side is higher than the floor at the beginning. Thus, the photons cannot regain all of the energy they lost, and they come out cooler than they were going in.

2 HOW DOES THE SUPERVOID FIT IN?

In 2015 astronomers discovered a supervoid about three billion light-years from Earth that they think might explain the cold spot. To understand why the two might be connected, it helps to visualize the universe as a set of nestled spheres. Space itself (*inner sphere*) is expanding outward, as is the point of origin of the CMB light (*outer sphere*), which was released about 13.8 billion years ago in the early universe. As this light traveled toward us, some of it crossed through the supervoid, where it might have lost energy and become colder because of the ISW effect 3.

Not to scale

Illustrations by Moonrunner Design

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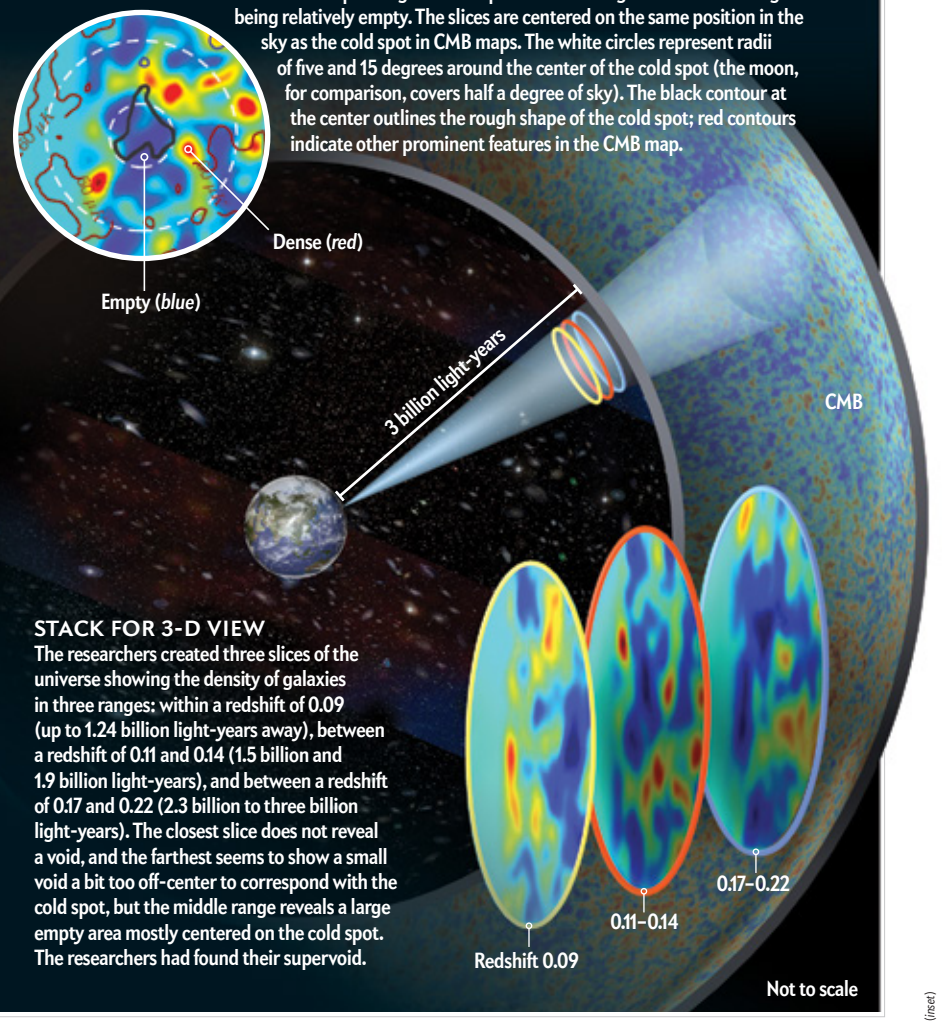
METHODOLOGY

Searching for a Supervoid

To look for a supervoid that could explain the cold spot, astronomers analyzed a catalog of galaxies created by the Wide-field Infrared Survey Explorer (WISE) satellite, the Two Micron All Sky Survey (2MASS) and Pan-STARRS. This catalog showed them the positions of many galaxies across the sky, but they needed to know how far away those galaxies were to determine if there was an empty spot in space. To assign distances, the researchers looked at the optical colors of each galaxy, which gave a rough estimation of how much its light had been "redshifted," or pushed toward the red end of the electromagnetic spectrum. This effect is caused by the expansion of the universe—when space stretches while light is traveling through it, the wavelength of the light photons stretches, too. The greater the redshift of a galaxy, the farther it lies from Earth. Combining the positions of the galaxies on the sky with their estimated distances, the scientists created a three-dimensional map of the density of galaxies throughout space in the direction of the cold spot.


SLICES OF THE UNIVERSE
The researchers separated their 3-D density map into a series of flat slices showing the spread of galaxies at various distances from Earth. In each slice (*left*), color indicates density, with red areas corresponding to dense spots with lots of galaxies and blue regions being relatively empty. The slices are centered on the same position in the sky as the cold spot in CMB maps. The white circles represent radii of five and 15 degrees around the center of the cold spot (the moon, for comparison, covers half a degree of sky). The black contour at the center outlines the rough shape of the cold spot; red contours indicate other prominent features in the CMB map.
Dense (*red*)
Empty (*blue*)
3 billion light-years
CMB
STACK FOR 3-D VIEW
The researchers created three slices of the universe showing the density of galaxies in three ranges: within a redshift of 0.09 (up to 1.24 billion light-years away), between a redshift of 0.11 and 0.14 (1.5 billion and 1.9 billion light-years), and between a redshift of 0.17 and 0.22 (2.3 billion to three billion light-years). The closest slice does not reveal a void, and the farthest seems to show a small void a bit too off-center to correspond with the cold spot, but the middle range reveals a large empty area mostly centered on the cold spot. The researchers had found their supervoid.
0.17–0.22
0.11–0.14
Redshift 0.09
Not to scale

SOURCE: "DETECTION OF A SUPERVOID ALIGNED WITH THE COLD SPOT OF THE COSMIC MICROWAVE BACKGROUND," BY ISTVÁN SZAPUDI ET AL., IN *MONTHLY NOTICES OF THE ROYAL ASTRONOMICAL SOCIETY*; VOL. 450, NO. 1; JUNE 11, 2015 (*inset*)

served, the larger the distance from us, the larger the physical area that was covered, and thus the more accurate the galaxy counts could be. Close to us, where the volume in our field was small, we had low statistical significance. Consequently, we had only about a 75 percent chance that the hint in the low galaxy count we saw close up indicated a supervoid—at scientific standards, this amounts to a mere glimmer of hope. To decide the matter, we needed to image a much larger area, essentially covering the full cold spot region. At the time, we could not obtain enough coverage with the telescopes available to us; Granett graduated with his Ph.D. and is now at the Astronomical Observatory of Brera in Italy, and Neyrinck went on to Johns Hopkins University.

A LUCKY BREAK

FORTUNATELY FOR ME, within a few years I would be able to obtain new data. About the time I was saying good-bye to Granett and Neyrinck, the Institute for Astronomy at the University of Hawaii, my home base, finished constructing a new telescope: PS1, the initial observatory for the Panoramic Survey Telescope and Rapid Response System (Pan-STARRS). It was exactly what I needed. Equipped with the world's largest camera, with 1.4 gigapixels, the telescope is located at 10,000 feet above sea level on the volcano Haleakala on Maui.

In May 2010, in a consortium with several other universities, my colleagues and I started to map three quarters of the sky with PS1. I remember trying to convince Nick Kaiser, then the principal investigator of Pan-STARRS, that we should map the cold spot area before anything else once the instrument was turned on. Although that did not happen, the region was within the area that was to be surveyed in the telescope's first few years, and the measurements I needed would come in little by little.

While we were eagerly awaiting these new data, I started working with then graduate student András Kovács to use the publicly available CMB observations from the Planck and WMAP satellites, along with a newly released galaxy data set

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based on observations in infrared light by NASA's Wide-field Infrared Survey Explorer (WISE) satellite to study the ISW effect and, if possible, to search for a supervoid.

Kovács visited me in Hawaii several times for a few months at a time, and during the summers I visited Budapest, where he was studying at Eötvös Loránd University. Otherwise, we had weekly teleconferences, and because of the 12-hour time delay between Honolulu and Budapest, we often had conversations that ran deep into the night in European time. During one of these early sessions, I asked him to find the largest low-density regions, or voids, in the WISE catalog of galaxies. A few days later he sent me an e-mail with images and coordinates of the biggest voids in the catalog. Reading his message, I immediately realized that one of the voids he found coincided with the same region of the sky where the cold spot is. I had not yet told Kovács of my interest in a link between a supervoid and the cold spot, and so the finding was doubly exciting to me: with Kovács not knowing to look for the cold spot connection, the finding could not have been biased by hope for evidence of a relation. Because WISE finds galaxies that are closer than those in the NVSS data set, this was the second clue that perhaps we should look for the supervoid nearby.

From this point, we worked for years to turn our initial clues into a discovery. We used a combined data set of galaxies from WISE, Pan-STARRS and the Two Micron All Sky Survey (2MASS), but we needed to assign distances to these galaxies. One way of measuring distance is to observe an object's "redshift"—the amount that its light has been shifted toward the red side of the electromagnetic spectrum. The farther away a galaxy is, the faster it recedes from us, and the greater its redshift is. Although we did not have access to precise redshift measurements for our galaxies, we could estimate their approximate redshifts by analyzing their colors, comparing our guesses of a galaxy's unredshifted brightness in various color bands with what we observed.

Finally, we could assign a distance to each galaxy in the direction of the cold spot, and we created a series of tomographic slices—flat pictures of the universe corresponding to different distances from Earth. The first set of images looked like vertical slices of an apple, revealing a supervoid that is approximately spherical and growing toward its center. It turns out this giant void has been hiding very near us, about three billion light-years away, which is why it was so hard to discover.

In the next few months we looked over the statistics of our data and found that the evidence for the supervoid is overwhelmingly significant—in other words, we are extremely assured of the existence of a low-density region aligned with the cold spot. And this supervoid, in fact, is huge: 1.8 billion light-years across, making it possibly the largest structure ever identified by humanity. It is probably a very rare object—cosmological theories suggest there should be only a few more of these within our observable universe.

UNDERSTANDING THE COLD SPOT

WE HAD FINALLY FOUND our supervoid. We knew from our earlier study that voids and clusters have a measurable effect on the CMB, producing small cold and hot spots. And the supervoid we found was indeed aligned with the most significant of anomalies in the CMB. Puzzle solved, right?

Not quite. The mere presence of the supervoid and even its alignment with the region of the cold spot are not enough to definitively conclude that one causes the other. They could be lined up by chance. Our analysis, though, conservatively estimates that the possibility that the supervoid created the cold spot is 20,000 times more likely than the chance that it was just a coincidence.

We have a bigger problem, however. Although the supervoid is in the right place to explain the cold spot, it is not quite the right size. To explain why the cold spot is so much cooler than the average CMB temperature, the supervoid would need to be even larger than it seems to be, perhaps by a factor of two to four. This discrepancy is so hard to stomach that some scientists think the fact that the supervoid overlaps with the area of the cold spot is merely a fluke. They suggest we look for other explanations, such as the possibility that galaxies are releasing less radiation into space than we expect—a phenomenon that could mimic the ISW effect to some extent. Also, although our observations clearly prove the existence of the supervoid, we cannot be sure enough of its size, shape and position to make precise calculations about the effect it should have. In particular, if the shape of the supervoid is elongated toward us, or if several spherical voids are stacked next to one another in the direction of the cold spot (like a snowman), then the void could more easily explain its presence. Thus, we do not yet know how much of a difficulty the size of the supervoid poses for our theory.

We need more data. Already we are planning to repeat our study for the full area of the sky that has been mapped with PS1, rather than the initial partial section, using observations that scientists have additionally refined to reduce uncertainties. With this data set we can quantify the divergence between our measurements and theory to determine whether it necessitates modifying our thinking about the ISW effect and voids. It may be that this discrepancy is telling us something interesting. For instance, a class of alternative theories of gravity that diverge from general relativity has a unique signature that would appear only in voids, and if one of these turns out to be correct, the ISW mechanism may operate differently as well. And if our supervoid has offered up a hint of these theories, we may have an exciting opportunity to understand the universe on a deeper level than we currently know.

No matter what, the discovery of the supervoid stands to tell us something significant about physics—perhaps it is proof of the existence of dark energy, or maybe it reveals an even more surprising truth about how gravity operates. In coming years we should know more about the supervoid and thus the nature of the universe we live in. SA

István Szapudi is an astronomer at the University of Hawaii's Institute for Astronomy who studies cosmology and the large-scale structure of the universe.

MORE TO EXPLORE

Detection of a Supervoid Aligned with the Cold Spot of the Cosmic Microwave Background. István Szapudi et al. in *Monthly Notices of the Royal Astronomical Society*, Vol. 450, No. 1, pages 288–294; June 11, 2015.

FROM OUR ARCHIVES

Is the Universe Out of Tune? Glenn D. Starkman and Dominik J. Schwarz; August 2005.

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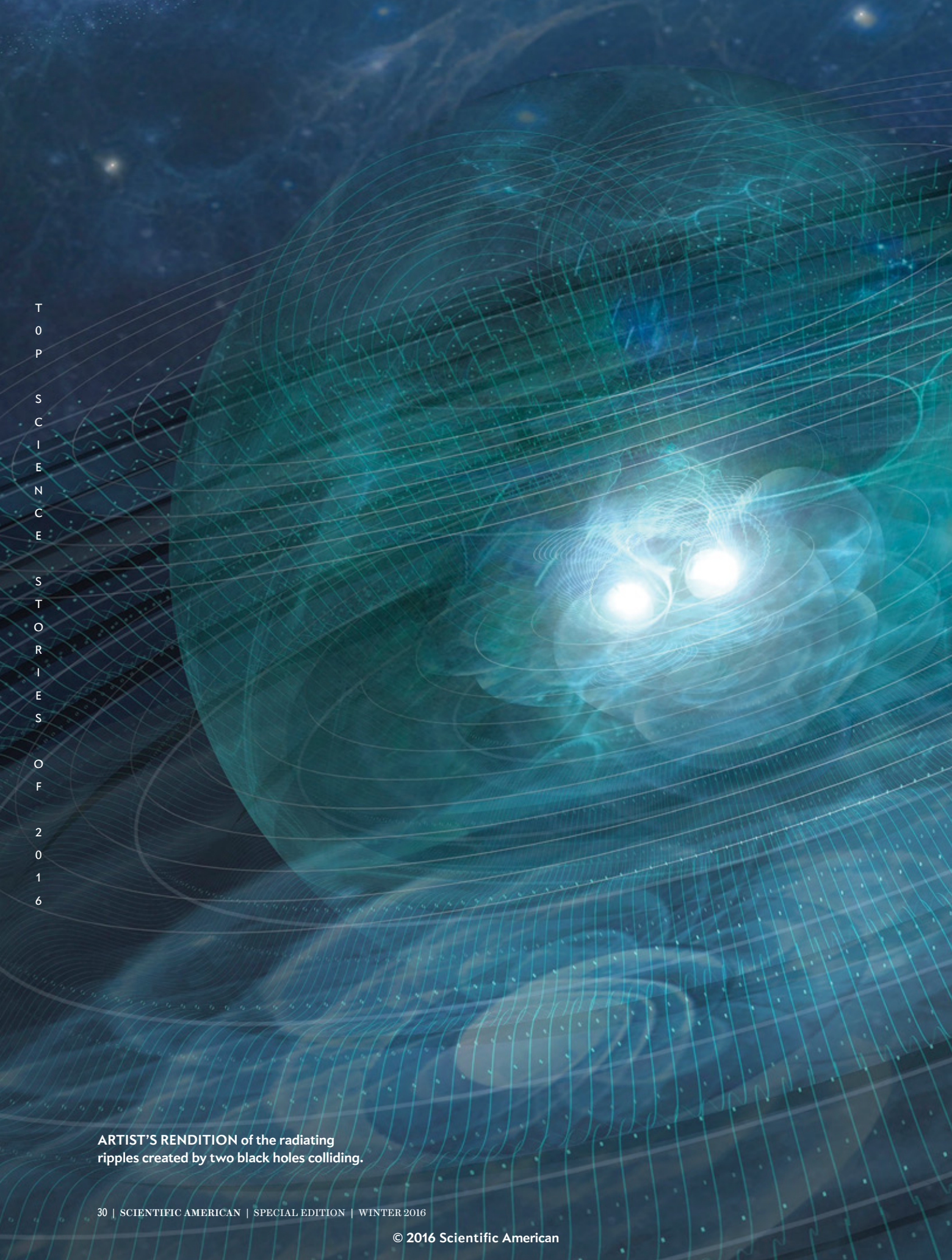

ARTIST'S RENDITION of the radiating ripples created by two black holes colliding.

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ASTROPHYSICS

RIPPLES *IN* SPACETIME

On February 11, 2016, scientists announced that a daring experiment had finally confirmed Einstein's 1916 prediction of gravitational waves. That day *Clara Moskowitz* explained why the discovery promises to open a new era in astrophysics

THE LASER INTERFEROMETER GRAVITATIONAL-WAVE OBSERVATORY (LIGO) has discovered ripples in spacetime created by merging black holes. About 1.3 billion years ago two black holes swirled closer and closer together until they crashed in a furious bang. Each black hole packed roughly 30 times the mass of our sun into a minute volume, and their head-on impact came as the two were approaching the speed of light. The staggering strength of the merger gave rise to a new black hole and created a gravitational field so strong that it distorted spacetime in waves that spread throughout space with a power about 50 times stronger than that of all the shining stars and galaxies in the observable universe.

Illustration by Moonrunner Design

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Such events are, incredibly, thought to be common in space, but this collision was the first of its kind ever detected and its waves the first ever seen. Scientists with the Laser Interferometer Gravitational-Wave Observatory announced today, at a much anticipated press conference in Washington, D.C. (one of at least five simultaneous events held in the U.S. and Europe), that the more than half-century search for gravitational waves had finally succeeded.

"This was truly a scientific moonshot, and we did it, we landed on the moon," LIGO executive director David Reitze said during the announcement.

"There are people who've put their entire life into this search, and there are people who died before having a chance to see anything," says LIGO team member Szabolcs Márka, a physicist at Columbia University. "It's really a wonderful feeling that you have validated the investment of the tremendous amount of work. And it's not just that you found something, but you gave something to everybody, to the rest of the human race."

"IT'S NOT JUST THAT YOU FOUND SOMETHING, BUT YOU GAVE SOMETHING TO EVERYBODY, TO THE REST OF THE HUMAN RACE."

—SZABOLCS MÁRKA, *Columbia University*

Albert Einstein first predicted gravitational waves in 1916 based on his general theory of relativity, but even he waffled about whether or not they truly exist. Scientists began seeking these ripples in spacetime in the 1960s, but none succeeded in measuring their effects on Earth until now. LIGO's discovery, accepted for publication in *Physical Review Letters*, not only provides the first direct evidence for gravitational waves but also opens the door to using them to study the powerful cosmic events that create them. "It's a huge deal," says Luis Lehner, a physicist at the Perimeter Institute for Theoretical Physics in Ontario who is not affiliated with the LIGO project. "It has pushed the fundamental theory of gravity forward in a very strong way and gives us an incredible tool to probe very deep questions of the universe."

"ONE OF THE MOST COMPLEX SYSTEMS EVER BUILT"

MORE THAN 1,000 SCIENTISTS work on the $1-billion LIGO experiment, which is funded by the National Science Foundation. The project uses two detectors, one located in Washington State and the other in Louisiana, to sense the distortions in space that occur when a gravitational wave passes through Earth. Each detector is shaped like a giant L, with legs four kilometers long. Laser light bounces back and forth through the legs, reflecting off mirrors, and amazingly precise atomic clocks measure how long it takes to make the journey. Typically the two legs are exactly the same length, and so the light takes exactly the same amount of time to traverse each. If a gravitational wave passes through, however, the detector and the ground underneath it will expand and contract infinitesimally in one direction, and the two perpendicular legs will no longer be the same size. One of the lasers will arrive a fraction of a second later than the other.

LIGO must be unbelievably sensitive to measure this change in the length of the legs, which is smaller than one ten-thousandth the diameter of a proton, or less than the size of a soccer ball compared with the span of the Milky Way. "It's one of the most complex systems ever built by mankind," Márka says. "There are so many knobs to turn, so many things to align, to achieve that [sensitivity]." In fact, the experiment is so delicate that unrelated events such as an airplane flying overhead, wind buffeting the building or tiny seismic shifts in the ground below the detector can disturb the lasers in ways that mimic gravitational signals. "If I clap in the control room, you will see a blip," says Imre Bartos, another member of the LIGO team at Columbia. The researchers carefully weed out such contaminating signals and also take advantage of the fact that the detectors in Washington and Louisiana are highly unlikely to be affected by the same contamination at the same time. "By comparing the two detectors, we can be even more certain that what we are seeing is something that's coming from outside Earth," Bartos adds.

LIGO began its first run in 2002 and hunted through 2010 without finding any gravitational waves. The scientists then shut down the experiment and upgraded nearly every aspect of the detectors, including boosting the power of the lasers and replacing the mirrors, for a subsequent run, called Advanced LIGO, that began officially on September 18, 2015. Yet even before then, the experiment was up and running: the signal arrived on September 14 at 5:51 A.M. Eastern time, reaching the detector in Louisiana seven milliseconds before it got to the detector in Washington. Advanced LIGO is already about three times more sensitive than the initial LIGO and is designed to become about 10 times more sensitive than the first iteration in the next few years.

LONG TIME COMING

BEFORE NOW, THE STRONGEST EVIDENCE of gravitational waves came indirectly from observations of superdense, spinning neutron stars called pulsars. In 1974 Joseph Taylor, Jr., and Russell Hulse discovered a pulsar circling a neutron star, and later observations showed that the pulsar's orbit was shrinking. Scientists concluded that the pulsar must be losing energy in the form of gravitational waves—a discovery that won Taylor and Hulse the 1993 Nobel Prize in Physics. Ever since this clue, astronomers have been hoping to detect the waves themselves. "I've certainly been looking forward to this event for a long time," Taylor says. "There is a long history, and I think projects that take this long to bear fruit require an awful lot of patience. It's about time."

IN BRIEF

On February 11, 2016, scientists at the Laser Interferometer Gravitational-Wave Observatory (LIGO) announced that they had successfully detected gravitational waves for the first time in history.

Before this discovery, evidence of gravitational waves had come indirectly from observations of pulsars. LIGO's detection is also the strongest confirmation to date for the existence of black holes.

LIGO will enable scientists to study black holes and other cosmic events, such as supernovae and neutron stars, in entirely new ways.

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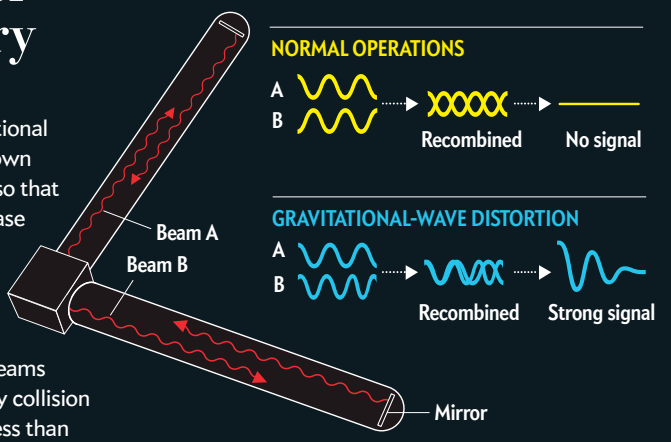
HOW IT WORKS

The Laser Interferometer Gravitational Observatory

LIGO EXPERIMENT uses two L-shaped detectors, one in Washington State and one in Louisiana, to search for gravitational waves. Each detector bounces laser light between mirrors down two perpendicular four-kilometer legs. LIGO splits the light so that the wave traveling through the first leg, Beam A, is out of phase with that in the other, Beam B. When the beams recombine (*yellow*), the waves should cancel each other out, rendering the resulting beam dark. If, however, a gravitational wave passes through Earth and changes the relative length of the legs (*blue*), the waves will not match up and the combined beams will reveal telltale beats. The effect is tiny, however—a nearby collision of two black holes will change the length of LIGO's legs by less than the diameter of a proton.



The discovery is not just proof of gravitational waves but the strongest confirmation yet for the existence of black holes. "We think black holes exist out there. We have very strong evidence they do, but we don't have direct evidence," Lehner says. "Everything is indirect. Given that black holes themselves cannot give any signal other than gravitational waves, this is the most direct way to prove that a black hole exists."

LIGO's ability to study the characteristics of gravitational waves will allow scientists to study black holes in a whole new way. Researchers would like to know the details of how two black holes collide and whether a new black hole arises as theory suggests. "We're talking about two objects that do not emit light—they're completely dark," says Janna Levin, a theorist at Barnard College who is outside the LIGO collaboration. "In the details of a collision and in terms of the gravitational waves, you could see the formation of a new black hole." The observatory should also be able to detect gravitational waves created by other cataclysmic events, such as exploding supernovae and collisions of two neutron stars.

LIGO and future gravitational wave experiments will also allow physicists to put general relativity to the test. The 100-year-old theory has stood the test of time, but it still conflicts with the theory of quantum mechanics that rules over the subatomic realm. "We know general relativity should show cracks at some point, and the way it shows them will guide our theory to one that is more complete," Lehner says. "This is pushing the theory over six orders of magnitude compared with the previous strongest test," which came from observations of pulsars.

LIGO is the first of many observatories that will join this new era of gravitational astronomy. A similar project, Advanced Virgo, will come online at the end of 2016 in Italy, and later this decade the Kamioka Gravitational Wave Detector (KAGRA) in Japan will begin observations. Ground-based telescope projects called pulsar timing arrays aim to study gravitational waves by noting delays in light from pulsars arriving on Earth after traveling through wave-stretched space. And a spacecraft called Lisa Pathfinder launched in December 2015 to test technology for a proposed space-based observatory that will be sensitive to longer-wavelength gravitational waves from supermassive black hole collisions.

"Every time you open a new window to the universe we always discover new things," Lehner says. "It's like Galileo pointing the first telescope to the sky. Initially he saw some planets and moons, but then as we got radio, UV and x-ray telescopes, we discovered more and more about the universe. We are pretty much at the moment where Galileo was beginning to see the first objects around Earth. It will have such a huge impact on the field." SA

Editor's note: *Since this article was written, the LIGO team announced the discovery of a second gravitational-wave signal, on June 15, 2016. The follow-up act also involved waves created by two crashing black holes—in this case, one about 14 times and the other about eight times the mass of the sun. These black holes' smaller masses, relative to the earlier pair LIGO detected, created waves of a higher frequency that the experiment could observe for longer, gathering a more detailed signal. Advanced LIGO finished its first run in January 2016 and shut down for upgrades; as we went to press, it was set to begin a new, six-month run around fall 2016. Meanwhile Europe's Advanced Virgo experiment is due to start up in late 2016, and a project in Japan and a detector in India are in the works.*

Clara Moskowitz is *Scientific American*'s senior editor covering space and physics. She has a bachelor's degree in astronomy and physics from Wesleyan University and a graduate degree in science journalism from the University of California, Santa Cruz.

MORE TO EXPLORE

Observation of Gravitational Waves from a Binary Black Hole Merger. B. P. Abbott et al. in *Physical Review Letters*, Vol. 116, Article 061102; February 11, 2016.
The Next Wave. Davide Castelvecchi in *Nature*, Vol. 531, pages 428–431; March 24, 2016.

FROM OUR ARCHIVES

Ripples in Spacetime. W. Wayt Gibbs; October 2002.

scientificamerican.com/magazine/sa

Graphic by Jen Christiansen

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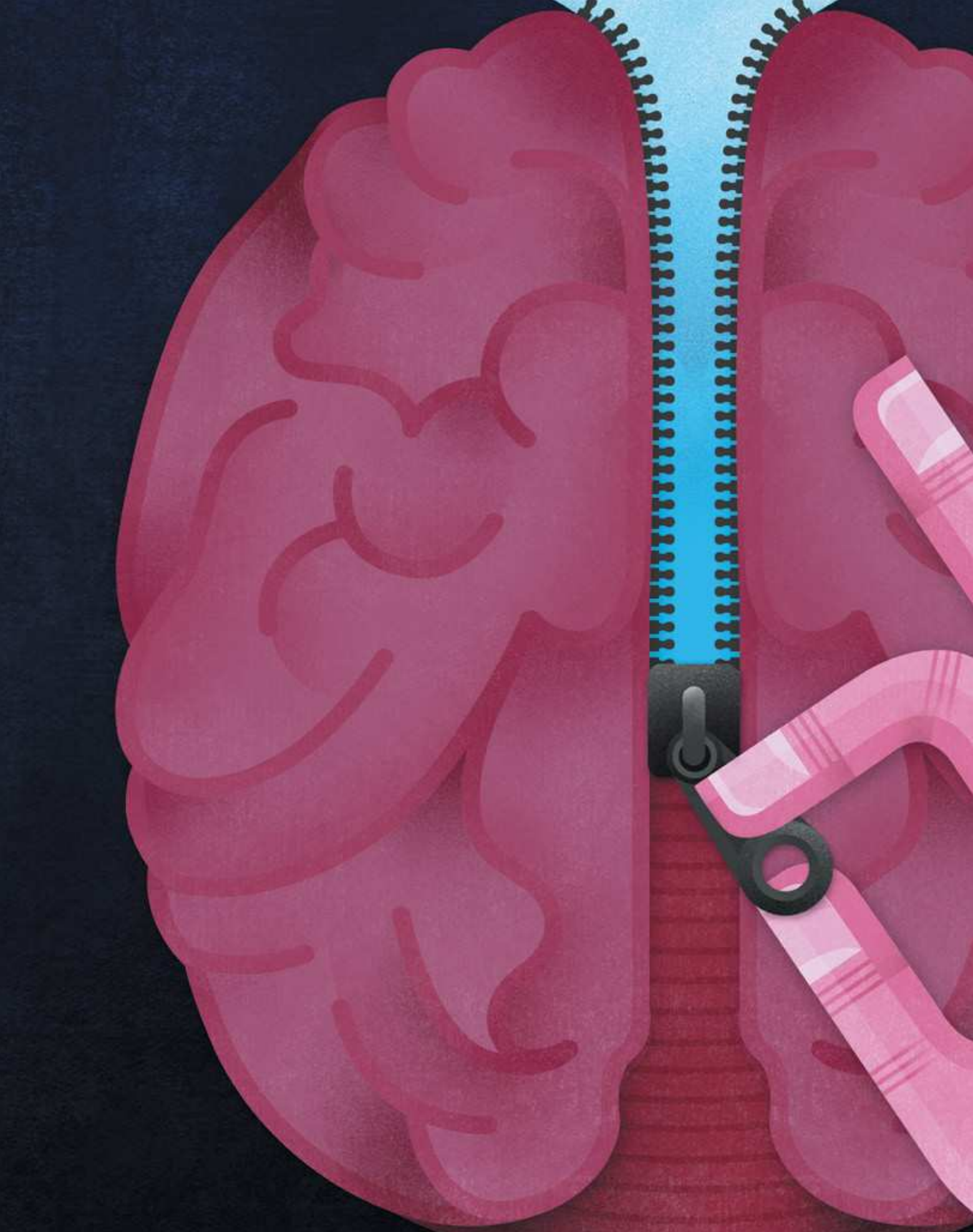

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MYSTERIES OF MIND AND BODY

Scientists have lately made remarkable discoveries about our physical and mental well-being—and things that threaten it. In the article leading this section, a pair of Nobel Prize winners explain an amazing brain system that functions like a GPS, tracking us from point to point on a mental grid (*page 36*). Another article follows disease detectives in early 2016 as they figured out that the recent explosion in Zika virus infections was not caused by genetic changes, as some feared; rather human activity is very likely at fault (*page 52*). Recently researchers have had groundbreaking wins against another scourge, successfully treating some cancer patients with therapies that boost immune responses against tumors; read about it on page 44. Efforts to slow aging look like they might be starting to bear fruit as well (*page 58*). Learn, too, about an astonishingly easy gene-editing technology that can change DNA within sperm and eggs, potentially transforming humanity as the changes get passed forward through generations. The technology raises unnerving questions about what we will do with such power (*page 64*).

Illustration by Maria Corte Maidagan

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NEUROSCIENCE

WHERE AM I? WHERE AM I GOING?

Scientists are discovering how the brain navigates

By May-Britt Moser and Edvard I. Moser

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Illustration by Viktor Koen

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OUR ABILITY TO PILOT A CAR OR AIRPLANE—OR EVEN TO WALK through city streets—has been completely transformed by the invention of the Global Positioning System (GPS). How did we navigate, though, before we had GPS? Recent work has shown that the mammalian brain uses an incredibly sophisticated GPS-like tracking system of its own to guide us from one location to the next. Like the GPS in our phones and cars, our brain's system assesses where we are and where we are heading by integrating multiple signals relating to our position and the passage of time. The brain normally makes these calculations with minimal effort, so we are barely conscious of them. It is only when we get lost or when our navigation skills are compromised by injury or a neurodegenerative disease that we get a glimpse of how critical this mapping-and-navigation system is to our existence.

The ability to figure out where we are and where we need to go is key to survival. Without it, we, like all animals, would be unable to find food or reproduce. Individuals—and, in fact, the entire species—would perish.

The sophistication of the mammalian system becomes particularly clear when contrasted to those of other animals. The simple roundworm *Caenorhabditis elegans,* which has just 302 neurons, navigates almost solely in response to olfactory signals, following the path of an increasing or decreasing odor gradient.

Animals with more sophisticated nervous systems, such as desert ants or honeybees, find their way with the help of additional strategies. One of these methods is called path integration, a GPS-like mechanism in which neurons calculate position based on constant monitoring of the animal's direction and speed of movement relative to a starting point—a task carried out without reference to external cues such as physical landmarks. In vertebrates, especially in mammals, the repertoire of behaviors that enable an animal to locate itself in its environment has expanded still further.

More than any other class of animals, mammals rely on the capacity to form neural maps of the environment—patterns of electrical activity in the brain in which groups of nerve cells fire in a way that reflects the layout of the surrounding environment and an animal's position in it. The formation of such mental maps is mostly thought to occur in the cortex, the brain's wrinkled upper layers that developed quite late in evolution.

Over the past few decades researchers have gained a deep understanding of just how the brain forms and then revises these maps as an animal moves. The recent work, conducted mostly in rodents, has revealed that the navigation systems consist of several specialized cell types that continuously calculate an animal's location, the distance it has traveled, the direction it is moving and its speed. Collectively these different cells form a dynamic map of local space that not only operates in the

IN BRIEF

Determining where we are in relation to our surroundings—streets, trees or other landmarks around us—remains an essential skill without which our own survival, or even that of our species, would rapidly be endangered.

Networks of cells lodged deep within the brain work together to assemble an internal mental map of our environment that enables us to find our way seamlessly from place to place, as if these cells equated to a biological Global Positioning System.

Regions of the brain involved with pathfinding are also intimately connected to the formation of new memories. When these neural tracts malfunction, they can produce the severe disorientation experienced by a patient with Alzheimer's disease.

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present but also can be stored as a memory for later use.

A NEUROSCIENCE OF SPACE

THE STUDY of the brain's spatial maps began with Edward C. Tolman, a psychology professor at the University of California, Berkeley, from 1918 to 1954. Before Tolman's work, laboratory experiments in rats seemed to suggest that animals find their way around by responding to—and then memorizing—successive stimuli along the path they move. In learning to run a maze, for instance, they were thought to recall sequences of turns they made from the maze's start to its end. This idea, however, did not take into account that the animals might visualize an overall picture of the entire maze to be able to plan the best route.

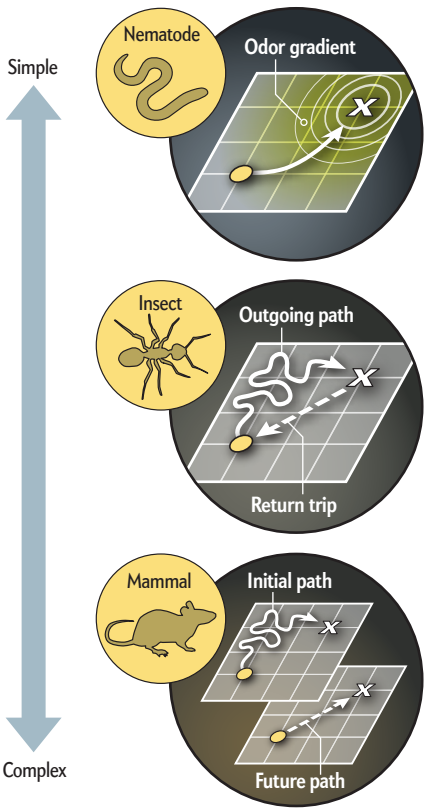
Tolman broke radically with prevailing views. He had observed rats take shortcuts or make detours, behaviors that would not be expected if they had learned only one long sequence of behaviors. Based on his observations, he proposed that animals form mental maps of the environment that mirror the spatial geometry of the outer world. These cognitive maps did more than help animals to find their way; they also appeared to record information about the events that the animals experienced at specific locales.

Tolman's ideas, proposed for the first time around 1930, remained controversial for decades. Acceptance came slowly, in part because they were based entirely on observing the behavior of experimental animals, which could be interpreted in many ways. Tolman did not have the concepts or tools to test whether an internal map of the environment actually existed in an animal's brain.

NATURE'S NAVIGATORS

The Nervous System's Incredible Pathfinding Skills

Survival for any species requires an ability to take into account the surrounding environment and to make a calculation, even a crude one, of where an animal has been, where it is and where it is going. On higher rungs of the evolutionary chain, many species have developed "path integration" systems that allow them to perform this task without the need to locate where they are by referencing external landmarks. Mammals have found an even more elaborate solution that uses internalized mental maps.



Tracing a Smell

The simple roundworm *Caenorhabditis elegans* exhibits perhaps the most basic animal navigation system. The worm world is organized according to smell. Equipped with a mere 302 neurons, it pushes itself straight ahead toward a food source by sensing ever increasing levels of an odor.

Internal GPS

Evolution has equipped even some insects and other arthropods with elaborate path-integration capabilities. They can monitor internally their speed and direction relative to a starting point. This allows them to find more efficient means of traveling a given route—a direct return instead of the zigs and zags traversed on an outbound journey.

Mental Maps

Mammals have evolved still more intricate orienteering skills in which neurons fire in their brain in sequences that mirror the routes they travel. These networks of neurons make up mental maps of the physical world. Animals store memories of past journeys and use them for the planning of future trips.

It took about 40 years before direct evidence for such a map appeared in studies of neural activity. In the 1950s progress in the development of microelectrodes made it possible to monitor electrical activity from individual neurons in awake animals. These very thin electrodes enabled researchers to identify the firing of single neurons as the animals went about their business. A cell "fires" when it triggers an action potential—a short-lasting change in the voltage across the neuronal cell membrane. Action potentials cause neurons to release neurotransmitter molecules that convey signals from one neuron to another.

John O'Keefe of University College London used microelectrodes to monitor action potentials in rats in the hippocampus, an area of the brain known for decades to be important for memory functions. In 1971 he reported that neurons there fired when a rat in a box spent time at a certain location—thus, he called them place cells. O'Keefe observed that different place cells fired at different locations in the box and that the firing pattern of the cells collectively formed a map of locations in the box. The combined activity of multiple place cells could be read out from the electrodes to identify the animal's precise location at any given time. In 1978 O'Keefe and his colleague Lynn Nadel, now at the University of Arizona, suggested that place cells were, in fact, an integral part of the cognitive map Tolman had envisaged.

A CORTICAL MAP

THE DISCOVERY of place cells opened a window into the deepest parts of the cortex, in areas farthest away from the sensory cortices (those that receive inputs from the senses) and from the motor cortex (which emits the signals that initiate or control movement). At the end of the 1960s, when O'Keefe started

Illustrations by Jen Christiansen

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his work, knowledge about when neurons switched on and off was largely restricted to areas called the primary sensory cortices, where neural activity was controlled directly by such sensory inputs as light, sound and touch.

Neuroscientists of that era speculated that the hippocampus was too far removed from the sensory organs to process their inputs in any manner that could easily be understood from a microelectrode recording. The discovery of cells in the hippocampus that created a map of an animal's immediate environment dashed that speculation.

Even though the finding was remarkable and suggested a role for place cells in navigation, no one knew what that role might be for decades after their discovery. Place cells were in an area of the hippocampus, called CA1, that was the end point in a signaling chain originating elsewhere in the hippocampus. It was hypothesized that place cells received many of the critical navigation-related computations from other hippocampal regions. In the early 2000s the two of us decided to explore this idea further in the new lab we had set up at the Norwegian University of Science and Technology in Trondheim. This pursuit ultimately led to a major discovery.

HUMANS AND OTHER MAMMALS FORM INTERNAL MAPS OF THE ENVIRONMENT—PATTERNS OF NEURAL ACTIVITY IN WHICH BRAIN CELLS FIRE TO REFLECT WHERE AN ANIMAL IS AND WHERE IT IS POSITIONED IN RELATION TO ITS SURROUNDINGS.

In collaboration with Menno Witter, now at our institute, and a set of highly creative students, we began by using microelectrodes to monitor the activity of place cells in the rat hippocampus after we had disrupted part of a neuronal circuit there known to feed information to these cells. We expected the work to confirm that this circuit was important to the proper functioning of the place cells. To our surprise, the neurons at the end of that circuit, in CA1, still fired when the animals arrived at specific locations.

Our team's inescapable conclusion was that place cells did not depend on this hippocampal circuit to gauge an animal's bearings. Our attention then turned to the only neural pathway that had been spared by our intervention: the direct connections to CA1 from the entorhinal cortex, an adjoining area that provides an interface to the rest of the cortex.

In 2002 we inserted microelectrodes in the entorhinal cortex, still in a collaboration with Witter, and began recording as the animals performed tasks that were similar to the ones we had used for our place cell studies. We guided electrodes into an area of the entorhinal cortex having direct connections to the parts of hippocampus where place cells had been recorded in almost every study before ours. Many cells in the entorhinal cortex turned out to fire when an animal was at a particular spot in the enclosure, much like the place cells in the hippocampus do. But unlike a place cell, a single cell in the entorhinal cortex fired, not only at one location visited by a rodent but at many.

The most striking property of these cells, though, was the way they fired. Their pattern of activity became obvious to us only when, in 2005, we increased the size of the enclosure in which we were recording. After expanding it to a certain size, we found that the multiple locations at which an entorhinal cell fired formed the vertices of a hexagon. At each vertex, the cell, which we called a grid cell, fired when the animal passed over it.

The hexagons, which covered the entire enclosure, appeared to form the individual units of a grid—similar to the squares formed by the coordinate lines on a road map. The firing pattern raised the possibility that grid cells, unlike place cells, provide information about distance and direction, helping an animal to track its trajectory based on internal cues from the body's motions without relying on inputs from the environment.

Several aspects of the grid also changed as we examined the activity of cells in different parts of the entorhinal cortex. At the dorsal part, near the top of this structure, the cells generated a grid of the enclosure that consisted of tightly spaced hexagons. The size of the hexagons increased in a series of steps—or modules—as one moved toward the lower, or ventral, part of the entorhinal cortex. The hexagonal grid elements in each module had a unique spacing.

The spacing of the grid cells in each successive module moving downward could be determined by multiplying the distance between cells in the previous module by a factor of about 1.4, approximately the square root of 2. In the module at the top of the entorhinal cortex, a rat that activated a grid cell at one vertex of a hexagon would have to travel 30 to 35 centimeters to an adjoining vertex. In the next module down, the animal would have to travel 42 to 49 centimeters, and so on. In the lowest module, the distance extended up to several meters in length.

We were extremely excited by the grid cells and their tidy organization. In most parts of the cortex, the neurons have firing patterns that appear chaotic and inaccessible, but here, deep in the cortex, there was a system of cells that fired in a predictable and orderly pattern. We were eager to investigate. But these cells and place cells were not the only ones involved in mapping the mammal's world—other surprises also awaited us.

Back in the mid-1980s and early 1990s, James B. Ranck of SUNY Downstate Medical Center and Jeffrey S. Taube, now at Dartmouth College, had described cells that fired when a rodent faced a particular direction. Ranck and Taube had discovered such head-direction cells in the presubiculum, another region of the cortex adjacent to the hippocampus.

Our studies found that these cells were also present in the entorhinal cortex, intermingled among grid cells. Many head-direction cells in the entorhinal cortex also functioned as grid cells: the locations in the enclosure where they fired also formed a grid, but the cells became active at those locales only when the rat was facing a certain direction. These cells appeared to provide a compass for the animal; by monitoring the cells, one could read out the direction the animal was facing at any given time relative to the surrounding environment.

A few years later, in 2008, we made a discovery in the entorhinal cortex of another cell type. These border cells fired whenever the animal approached a wall or an edge of the enclosure or some other divide. These cells appeared to calculate

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how far the animal was from a boundary. This information could then be used by grid cells to estimate how far the animal had traveled from the wall, and it could also be established as a reference point to remind the rat of the wall's whereabouts at a later time.

Finally, in 2015, yet a fourth kind of cell entered the scene. It responded specifically to the running speed, regardless of the animal's location or direction. The firing rates of these neurons increased in proportion to the speed of movement. Indeed, we could ascertain how fast an animal was moving at a given moment by looking at the firing rates of just a handful of speed cells. In conjunction with head-direction cells, speed cells may serve the role of providing grid cells continually updated information about the animal's movement—its speed, direction and the distance from where it started.

FROM GRID TO PLACE CELLS

OUR DISCOVERY of grid cells grew out of our desire to uncover the inputs that allow place cells to give mammals an internal picture of their environment. We now understand that place cells integrate the signals from various types of cells in the entorhinal cortex as the brain attempts to track the route an animal has traveled and where it is going in its environment. Yet even these processes do not tell the whole story of how mammals navigate.

Our initial work focused on the medial (inner) entorhinal cortex. Place cells may also receive signals from the lateral entorhinal cortex, which relays processed input from a number of sensory systems, including information about odor and identity of objects. By integrating inputs from the medial and lateral parts of the entorhinal cortex, place cells interpret signals from throughout the brain. The complex interaction of messages arriving in the hippocampus and the formation of location-specific memories that this enables are still being investigated by our lab and others, and this research will undoubtedly continue for many years to come.

One way to begin to understand how the spatial maps of the medial entorhinal cortex and the hippocampus combine to aid navigation is to ask how the maps differ. John Kubie and the late Robert U. Muller, both at SUNY Downstate Medical Center, showed in the 1980s that maps in the hippocampus made up of place cells may change entirely when an animal moves to a new environment—even to a different colored enclosure at the same location in the same room.

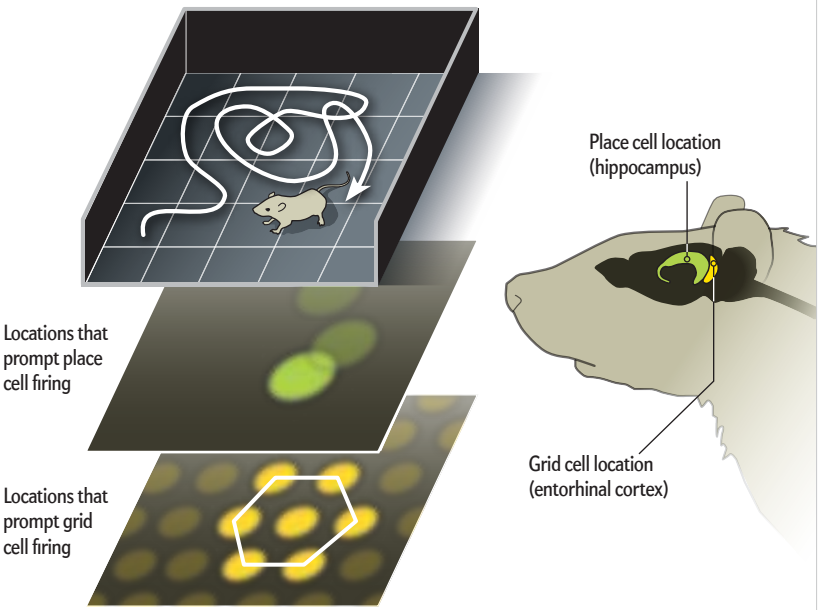
Experiments performed in our own lab, with rats foraging in up to 11 enclosures in a series of different rooms, have shown that each room, in fact, rapidly gives rise to its own independent map, further supporting the idea that the hippocampus forms spatial maps tailored to specific environments.

In contrast, the maps in the medial entorhinal cortex are universal. Grid cells—and head-direction and border cells—that fire together at a particular set of locations on the grid map for one environment also fire at analogous positions on the map for another environment—as if latitude and longitude lines from the first map were imposed on the new setting. The sequence of cells that fire as the animal moves northeast in one room of the cage repeats when the rat goes in that same direction in the other room. The pattern of signaling among these cells in the entorhinal cortex

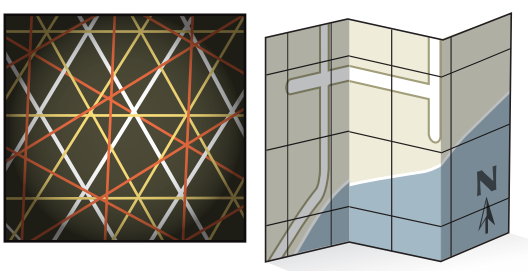
NEUROCARTOGRAPHY

How the Brain Takes Its Bearings

The idea that the brains of mammals make a mental map that mirrors the spatial geometry of the outer world first emerged around 1930. Neuroscientists have subsequently identified cells that work together to create such maps. A key development came in 1971, when an American-British researcher found that place cells in the rat hippocampus fire at particular locations on the willy-nilly path an animal travels. In 2005 the authors discovered grid cells that let an animal measure its location in its environment—say, in relation to the walls of an enclosure. As the animal moves about, each grid cell fires at multiple locations that correspond to the vertices of a hexagon.



A Cognitive Map Emerges
Firing of grid cells produces a map (*right*), akin to a geographical map (*far right*). Together with place cells that identify the animal's location in a particular environment, grid cells enable the animal to build a mental picture of its surroundings.



SOURCE: "SCIENTIFIC BACKGROUND: THE BRAIN'S NAVIGATIONAL PLACE AND GRID CELL SYSTEM," BY OLE KIEHN AND HANS FORSSBERG, WITH ILLUSTRATIONS BY MATTIAS KARLÉN. NOBELPRIZE.ORG, NOBEL MEDIA AB, 2014 www.nobelprize.org/nobel_prizes/medicine/laureates/2014/advanced.html (top)

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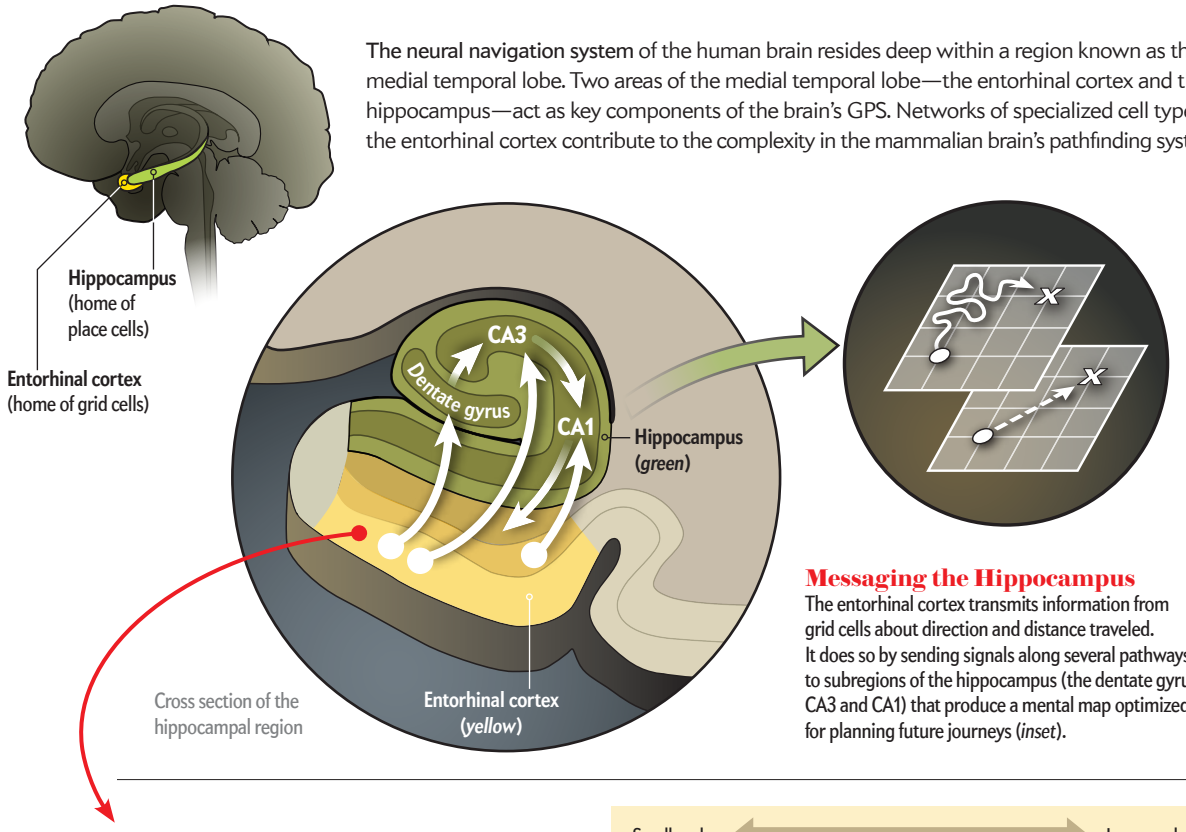
A PARTS LIST

Inside the Brain's GPS

The neural navigation system of the human brain resides deep within a region known as the medial temporal lobe. Two areas of the medial temporal lobe—the entorhinal cortex and the hippocampus—act as key components of the brain's GPS. Networks of specialized cell types in the entorhinal cortex contribute to the complexity in the mammalian brain's pathfinding system.

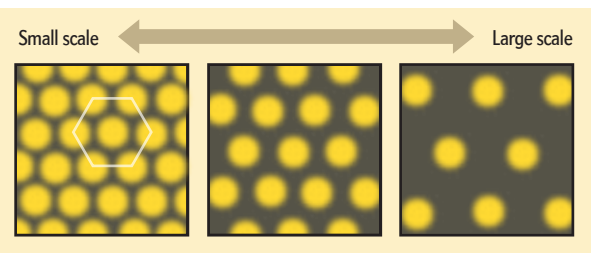


Messaging the Hippocampus

The entorhinal cortex transmits information from grid cells about direction and distance traveled. It does so by sending signals along several pathways to subregions of the hippocampus (the dentate gyrus, CA3 and CA1) that produce a mental map optimized for planning future journeys (*inset*).

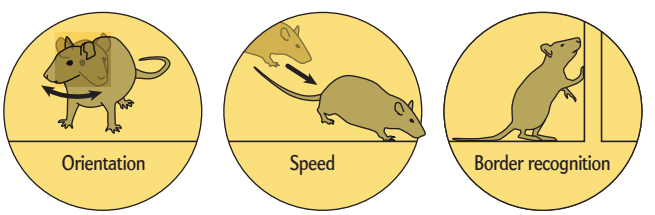
A Close Look at Grid Cell Organization …

… reveals that the spacing of the hexagonal elements that aid in creating a spatial map change when moving from top to bottom in the entorhinal cortex. The broader spacings correspond to larger distances the rat needs to travel to activate a vertex on the grid. At the top of the entorhinal cortex, a rat that activates a grid cell at one vertex of a hexagon will have to move 30 to 35 centimeters to an adjoining vertex. At the bottom, the animal needs to go as far as several meters.



Other Specialized Cells Recently Discovered …

… in the entorhinal cortex of rodents convey information to the hippocampus about the orientation of an individual's head, its speed of movement, and the distance to walls and other obstacles encountered. The output of these cells is combined to help create a composite map of the animal's environs.



is what the brain uses for navigating through its surroundings.

These codes are then transmitted from the entorhinal cortex to the hippocampus, where they are used to form maps specific to a particular place. From the standpoint of evolution, two sets of maps that integrate their information to guide animals appear to be an efficient solution for a system used by animals for spatial navigation. The grids formed in the medial entorhinal cortex that measure distance and direction do not change from one room to the next. In contrast, the place cells of the hippocampus form individual maps for every single room.

LOCAL MAPS

UNDERSTANDING the neural navigation system remains a work in progress. Almost all our knowledge of place and grid cells has been obtained in experiments in which electrical activity from neurons is recorded when rats or mice walk about randomly in highly artificial environments—boxes with flat bottoms and no internal structures to serve as landmarks.

A lab differs substantially from natural environments, which change constantly and are full of three-dimensional objects. The reductionism of the studies raises questions about whether

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place cells and grid cells fire in the same way when animals find themselves outside the lab.

Experiments in complex mazes that try to mimic animals' natural habitat provide a few clues to what might be going on. In 2009 we recorded grid cells as animals moved through an intricate maze in which they encountered a hairpin turn at the end of each alley that marked the beginning of the next passageway. The study showed that, as expected, grid cells formed patterns of hexagons to map out distances for the rats in individual alleys of the maze. But each time an animal turned from one alley to the next, an abrupt transition occurred. A separate grid pattern was then superimposed on the new alley, almost as if the rat were entering an entirely different room.

Later work in our lab has shown that grid maps also fragment into smaller maps in open environments if these spaces are large enough. We are now researching how these smaller maps merge to form an integrated map of a given area. Even these experiments are oversimplified because the enclosures are flat and horizontal. Experiments performed in other labs—observing flying bats and rats that climb around in cages—are beginning to provide some clues: place cells and head-direction cells seem to fire in specific places throughout any three-dimensional space, and most likely grid cells do as well.

SPACE AND MEMORY

THE NAVIGATIONAL SYSTEM in the hippocampus does more than help animals get from point A to point B. Beyond receiving information about position, distance and direction from the medial entorhinal cortex, the hippocampus makes a record of what is located in a particular place—whether a car or a flagpole—as well as the events that take place there. The map of space created by place cells thus contains not only information about an animal's whereabouts but also details about the animal's experiences, similar to Tolman's conception of a cognitive map.

Some of this added information appears to come from neurons in the lateral part of the entorhinal cortex. Particulars about objects and events fuse with an animal's coordinates and are laid down as a memory. When the memory is later retrieved, both the event and the position are called to mind.

This coupling of place with memory recalls a strategy for memorization invented by the ancient Greeks and Romans. The "method of loci" lets a person memorize a list of items by imagining putting each item at a position along a well-known path through a place, say, a landscape or a building—an arrangement often called a memory palace. Participants in memory contests still use the technique to recall long lists of numbers, letters or playing cards.

Sadly, the entorhinal cortex is among the first areas to fail in people with Alzheimer's disease. The illness causes brain cells there to die, and a reduction in its size is considered a reliable measure for identifying at-risk individuals. The tendency to wander and get lost is also among the earliest indicators of the disorder. In the later stages of Alzheimer's, cells die in the hippocampus, producing an inability to recall experiences or remember concepts such as the names of colors. In fact, a recent study has provided evidence that young individuals with a gene that places them at an elevated risk for Alzheimer's may have deficiencies in the functioning of their grid cell networks—a finding that may lead to new ways of diagnosing the disease.

A RICH REPERTOIRE

TODAY, MORE THAN 80 YEARS since Tolman first proposed the existence of a mental map of our surroundings, it is clear that place cells are just one component of an intricate representation the brain makes of its spatial environment to calculate location, distance, speed and direction. The multiple cell types that have been found in the navigation system of the rodent brain also occur in bats, monkeys and humans. Their existence across mammalian taxonomic orders suggests that grid and other cells involved in navigation arose early in the evolution of mammals and that similar neural algorithms are used to compute position across species.

Many of the building blocks of Tolman's map have been discovered, and we are beginning to understand how the brain creates and deploys them. The spatial representation system has become one of the best-understood circuits of the mammalian cortex, and the algorithms that it uses are starting to be identified to help unlock the neural codes the brain uses for navigation.

As with so many other areas of inquiry, new findings raise new questions. We know that the brain has an internal map, but we still need a better understanding of how the elements of the map work together to produce a cohesive representation of positioning and how the information is read by other brain systems to make decisions about where to go and how to get there.

Other questions abound. Is the spatial network of the hippocampus and the entorhinal cortex limited to navigation of local space? In rodents, we examine areas that have radii of only a few meters. Are place and grid cells also used for long-distance navigation, such as when bats migrate hundreds or thousands of kilometers?

Finally, we wonder how grid cells originate, whether there is a critical formative period for them in an animal's development and whether place and grid cells can be found in other vertebrates or invertebrates. If invertebrates use them, the finding would imply that evolution has used this spatial-mapping system for hundreds of millions of years. The brain's GPS will continue to provide a rich trove of leads for new research that will occupy generations of scientists in the decades ahead. SA

May-Britt Moser and **Edvard I. Moser** are professors in psychology and neuroscience at the Norwegian University of Science and Technology in Trondheim. The two co-founded the Kavli Institute for Systems Neuroscience in 2007 and the Center for Neural Computation in 2013, both located at the university. In 2014 they shared the Nobel Prize in Physiology or Medicine with John O'Keefe of University College London for the discovery of the brain's positioning system.

MORE TO EXPLORE

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FROM OUR ARCHIVES

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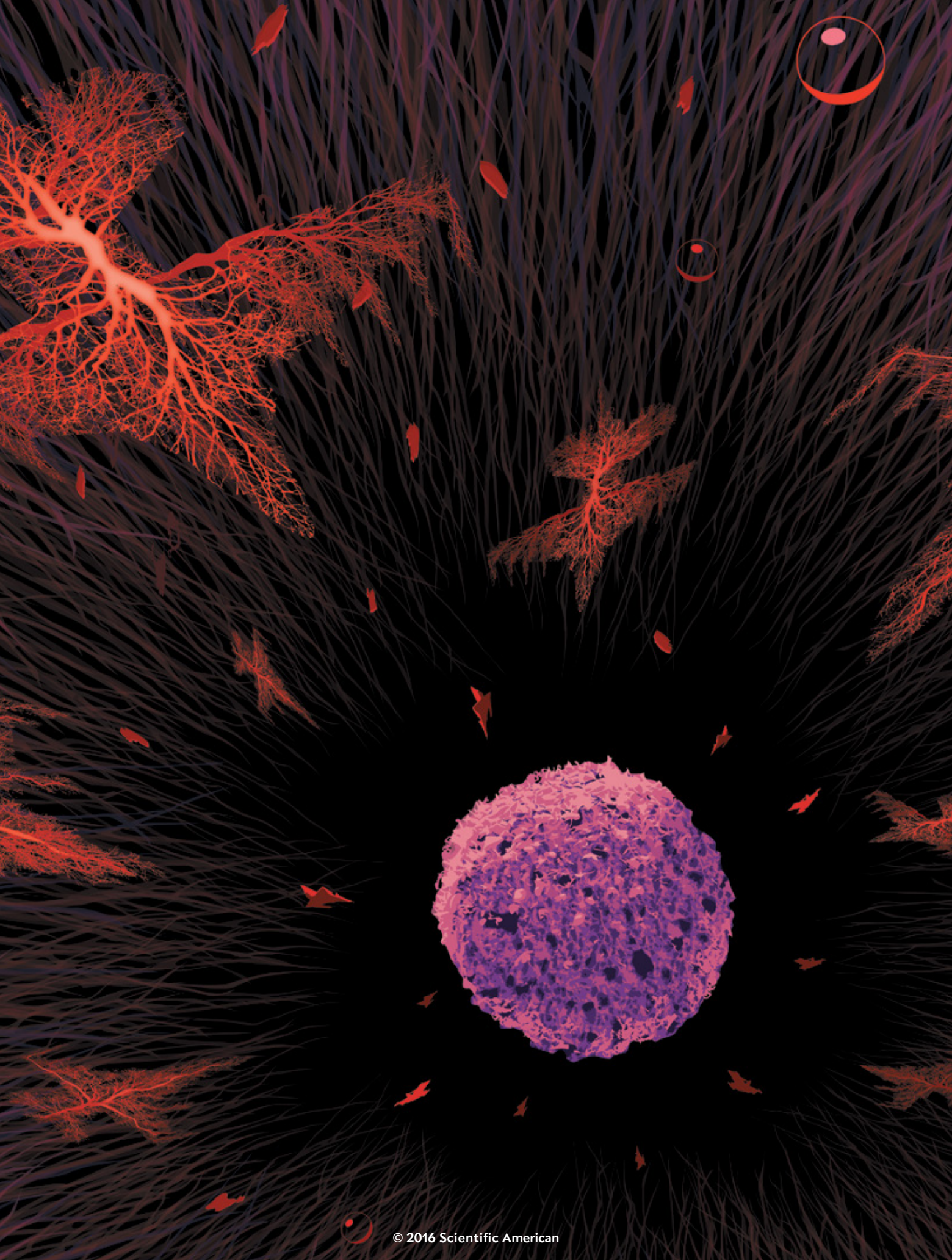

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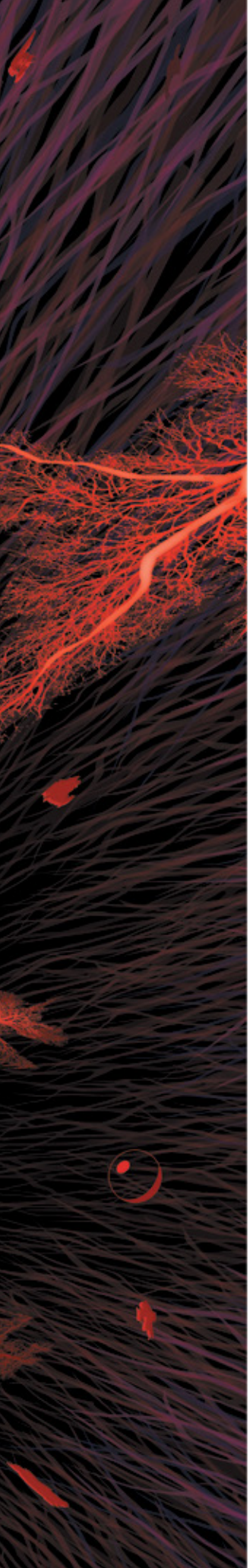

THE FUTURE OF MEDICINE

THE CANCER DEFENSE

Enhancing the body's own immune system is leading to promising results in the battle against malignancy

By Karen Weintraub

If Michelle Boyer had received her diagnosis of advanced and aggressive skin cancer in 2010 instead of 2013, she would almost certainly be dead by now. Melanoma, the most lethal form of skin malignancy, had spread from a mole on her back to her lungs, and she knew her prognosis was grim. But beginning in May 2013, the now 29-year-old Seattle resident started a series of revolutionary treatments—some of which first became available in 2011—that prompted her immune system to identify, attack and shrink the tumors. Although Boyer still has cancer and the immune-boosting drugs have taken a toll on her body, she is grateful to be alive and hopes that either her current course of therapy or the next one will eventually give her the kind of miraculous results that other patients have talked about on the Internet. "At this point, this is my life," she says. "People think it would be really hard to stay positive, but because to me it seems normal, it's not as much effort as you would think."

Karen Koehler, 59, a retired special education teacher from Park Ridge, N.J., may have won the immunotherapy jackpot on her first try. She has apparently been cured of a different kind of cancer—in her case leukemia—after a single infusion, in early 2015, with some of her own immune cells that had been genetically altered to fight her malignancy more aggressively. The treatment, which lasted a couple of hours, landed her in intensive care for several days because her revved-up immune system shifted so far into overdrive. This setback was followed by weeks in a regular hospital bed. But within a month after her treatment, scans showed no signs of cancer anywhere in her body.

Boyer and Koehler are two of the thousands of cancer patients who have undergone various kinds of immunotherapy over the past five years. Their experiences illustrate both the promise and the challenges of this fundamentally new approach to treating cancer—one that, instead of dousing the body with toxic chemicals or radiation from the outside to kill cancer cells, energizes the complex and highly interactive cells and molecular signals of its defense networks to do the job from the inside. The results so far have been encouraging; immunotherapy is quickly becoming a pillar—along with surgery, radiation and chemotherapy—of treatment for some cancers.

Illustration by Daniel Hertzberg

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In clinical trials of a new immunotherapy for a highly aggressive form of leukemia, 90 percent of patients underwent a complete remission: doctors could find no evidence of their disease anywhere in their body. Although some may eventually suffer a return of their cancer, for many others the response appears to be a permanent cure. In other trials, more than half of patients with advanced melanoma who received immunotherapy can now count their life expectancy in years instead of months. Immunotherapy, says Gary Gilliland, president and director of the Fred Hutchinson Cancer Research Center in Seattle, "is truly paradigm shifting in our approach to treating cancer."

These are, admittedly, still early days. Increasing life expectancy to a few years for some cancers still means that patients die of the disease. So scientists continue to experiment with different ways to unleash and boost the immune response, including vaccines, viruses, genetically engineered cells and pills [*see box on page 50*]. They are also beginning to combine these approaches to see if they can help more patients, perhaps with fewer side effects. But there is no longer any doubt that physicians can tap the immune system to beat cancer at least some of the time. "[We are at] the end of the beginning" of the immunotherapy story, says Eric Rubin, vice president of global clinical oncology for Merck Research Laboratories.

LIQUID SUCCESS

THE DREAM of fighting cancer with the immune system dates back at least 125 years to William Coley of New York City, a physician who injected some of his cancer patients with bacteria in an effort to jump-start their body's natural healing powers. Coley's approach was taken up by a few other doctors initially. But it gradually fell out of favor after his death in 1936, to be replaced by advances in chemotherapy and later hormone and antibody treatments, which showed more consistent results in a larger number of patients.

The idea of boosting the immune system, however, has never entirely lost its appeal, promoted in part by the Cancer Research Institute, a New York City–based philanthropy started in 1953 by Coley's daughter. In recent decades, as molecular biology has enhanced researchers' understanding of the immune system, how it works and when it fails, cancer investigators have restocked their arsenal with more potent immunological weapons.

Among the most attractive targets for those weapons have been cancers of the circulatory and lymphatic systems, such as leukemia and lymphoma. These diseases occur when various kinds of progenitor cells called stem cells, which normally give rise to red and white blood cells (among other tissues) instead mutate and grow uncontrollably, crowding out healthy cells and robbing the body of their vital functions. Many of these so-called liquid tumors form when something goes wrong with a part of the immune system called B cells. Normally B cells generate antibodies against bacteria and viruses. (B cells also help to coordinate various other immune responses, along with another group of cells called T cells.) But when B cells become cancerous, they destroy the body from the inside out.

In the late 20th century investigators developed the biological equivalent of a guided missile that attached itself to a B cell protein (CD20) found on the surface of these cells at a specific, late stage of their existence. Dubbed rituximab, this so-called monoclonal antibody signaled the T cells to do something they do not usually do: attack and destroy these older, CD20-bearing B cells.

The problem was that CD20 is not a cancer-specific marker. It appears on normal B cells as well as dangerous ones. So the drug killed both healthy and cancerous B cells. It turns out, however, that most people can live without B cells. (The same is not true of T cells, as the death of millions of people infected with the T cell–targeting AIDS virus tragically demonstrates.) And after the drug wore off, most patients eventually started making B cells on their own again from the stockpile of stem cells in their bone marrow. Clinical trials in the 1990s demonstrated that the combination of chemotherapy and rituximab was particularly effective against B cell–based cancers.

Koehler's leukemia originated with mutated B cells, but rituximab made her very sick and seemed only partially effective, so she stopped taking it. In addition, tests indicated her cancer would resist standard chemotherapy. Because her malignancy was rapidly getting worse, her doctors suggested an experimental immune treatment custom-designed to fight her form of leukemia. She agreed.

The goal of the new treatment was to destroy all of Koehler's B cells, as rituximab would, but with two key differences. A different protein (CD19) on the B cells was the objective. And rather than using an added drug to paint a target on that protein for T cells that were already in Koehler's body, doctors took a more direct approach. They removed some of her T cells and genetically engineered them to attack CD19 automatically, without any prompting.

Investigators call these turbocharged cells chimeric antigen receptor T cells, or CAR-T. They display some of the characteristics of both T cells and B cells in much the same way that ancient mythological creatures called chimeras were supposed to be made up of different animals. CAR-T therapy is still experimental, but the U.S. Food and Drug Administration is expected to consider approving the treatment for general use sometime in 2017.

The CD19-targeting CAR-T cells multiplied so quickly inside Koehler's body that the single bag of modified cells that she received on February 10, 2015, knocked out all her B cells. Unlike other patients, however, her body seems to have forgotten how to make healthy B cells. Fortunately, there is a work-around: every month she gets an hours-long infusion of artificial antibodies, called gamma globulin, to help protect her against infection. The infusions are a time-consuming hassle, she says, but "it's not chemo, so I'll take it."

CAR-T therapy did hit Koehler with something that can be worse than chemo's nausea—a storm called cytokine release syn-

IN BRIEF

A new generation of treatments that boost the immune system's ability to both fight and control malignant cells indefinitely have achieved remarkable results over the past five years. **Thousands of people** with aggressive and advanced lung and skin cancers, as well as various kinds of leukemia and lymphoma, have been treated—and many of them have seemingly been cured. **Investigators are developing** new regimens and combinations of treatments that may prove safer and more effective than current approaches in the next few years.

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MICHELLE BOYER (*1*) learned in 2013 that she had advanced skin cancer. After six courses of immunotherapy, she is still not cured but is living longer than her doctors initially thought possible. Karen Koehler (*2*) remains free of cancer a year after receiving an infusion of her own immune cells, which had been genetically engineered to eradicate her leukemia.

drome. This reaction occurs when many more T cells than usual are activated at once—triggering a flood of chemical signals, called cytokines, that the immune system uses to communicate. The result can be a life-threatening frenzy of activity, in which immune cells destroy healthy tissues, causing multiorgan failure.

For Koehler, the storm came on hard and fast. She felt terrible within an hour of receiving her own altered T cells. By that night she was in intensive care where she remained for eight days—half of that time she was in a coma and totally unresponsive. She has no memory of what transpired then but can recall the hallucinations of a few days later, when she asked nurses for help packing lunch for a pair of famous golfers. Koehler has been addicted to golf since 1999, when she took it up as a way to meet men, including the man who later became her husband.

By the time Koehler got out of the hospital in early March 2015, she was incredibly weak but rebounding fast. A bone marrow test showed no evidence of cancer, and three weeks after that she was back on the golf course with her husband. The cytokine storm was terrible, but unlike chemo, the effects subsided within a few weeks and did not cause her to lose her hair. Fortunately, given that cytokine storms are fairly common with CAR-T cell treatments, physicians have begun to learn just how far to push patients like Koehler to get the greatest benefit without risking their lives.

CAR-T cell therapy must be custom-designed and produced for each patient. Manufacturing them for all the leukemia and lymphoma patients who might want them will be a challenge, as well as extraordinarily expensive—although it is too soon to know exactly how much CAR-Ts will cost because they have been used only in academic research so far. Robert Preti, founder of PCT, a CAR-T manufacturer, is working to improve the production process; he believes these are mainly engineering issues that will be solved with a few more years of hard work.

The other major challenge facing CAR-T treatment is translating its success from liquid cancers to solid tumors—the kind that forms lumps in the breast, prostate, lung, skin and other tissues. One stumbling block is that CAR-T cells have a hard time leaving the bloodstream to find a solid tumor, explains Ira Mellman, who is vice president of cancer immunology at Genentech. In the blood, the liquid tumor cells are relatively easy to locate. Even more crucial, whereas CAR-Ts can eliminate B cells in blood and lymph cancers, there is no comparable cell in solid tumors that patients can live without.

SOLID STATE

SOLID TUMORS pose other difficulties for immune treatments. They are often surrounded by a matrix of connective and other tissues, which blocks cells from entering the malignant mass. In addition, the internal pressure of a solid tumor is typically higher than its surroundings, which tends to flush out the chemical signals that the immune system uses to flag aberrant cells—not to mention many drugs.

Yet these tumors have shown some vulnerability. In 2011 the FDA approved a monoclonal antibody called ipilimumab to treat advanced cases of melanoma. Unlike traditional therapy, ipilimumab is not designed to kill tumors directly; rather it releases the biological brakes that some cancers are able to clamp on the immune system, freeing the body's defenses to do a better job.

Melanoma has a nasty habit of defrauding immune system

Photograph by Annie Marie Musselman (1), Photograph by Amy Eckert (2)

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Three Immune Strategies

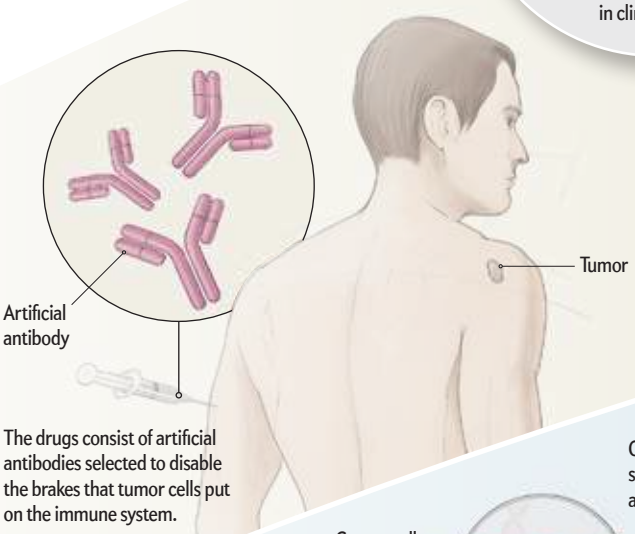
Surgery, radiation and chemotherapy have long served as the standard treatments against cancer. But clinical trials over the past five years have shown that supercharging the body's immune cells—which evolved to fight harmful bacteria and viruses, among other things—offers a powerful new addition to the mix by helping the cells to find and destroy tumors. The approaches shown here are being tested alone or in combination with other treatments.

How is immunotherapy changing the treatment of solid tumors?

Cancers of the skin, lungs and other tissues are called solid tumors because they form a mass that creates its own protective environment. Checkpoint inhibitors help to disrupt this environment, eliminating advanced skin tumors for one in five patients in clinical trials.

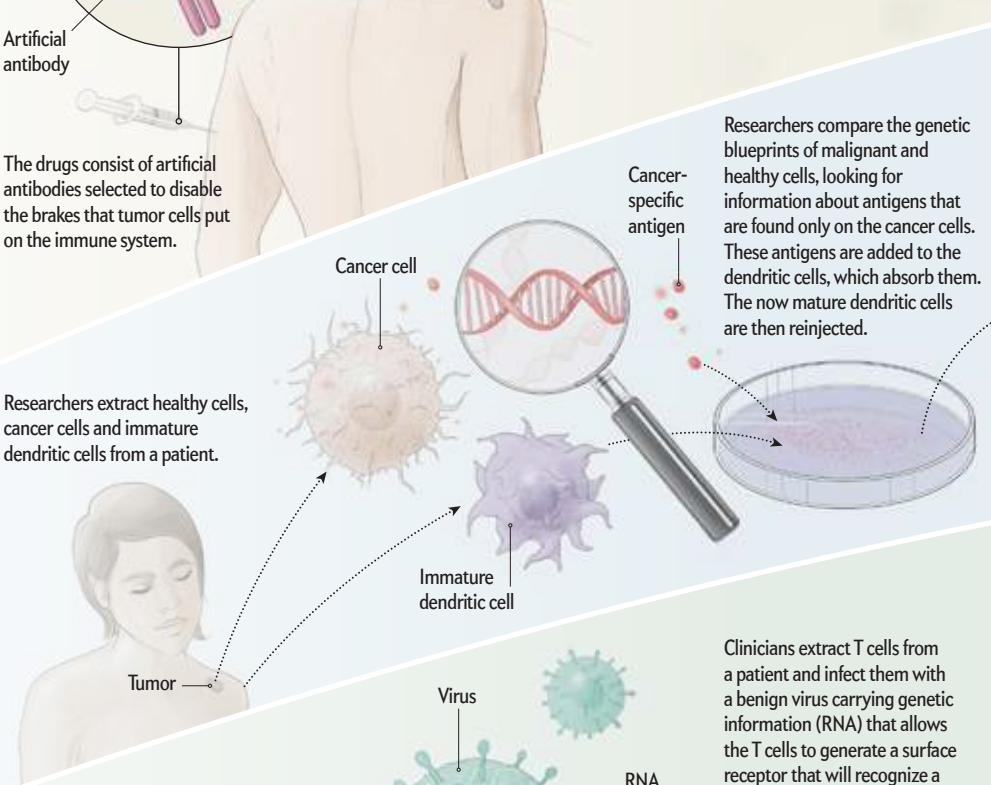
Checkpoint Inhibitors

Left unchecked, immune responses can be so powerful that they will destroy healthy tissue. Thus, specialized immune cells called T cells must pass several biological checkpoints before achieving full strength. Cancer cells often act on these checkpoints in a way that prevents the immune system from attacking the tumor. New drugs—called checkpoint inhibitors—disable the cancer cells' immune-dampening signals, allowing the immune system to do its job.


Normal checkpoint detector protein
Tumor protein that quiets T cells
Artificial antibody
Tumor
Many cancer cells hide from the immune system by displaying specific proteins that tell nearby T cells not to advance to the next stage of activation and, essentially, to leave the tumor alone.
The drugs consist of artificial antibodies selected to disable the brakes that tumor cells put on the immune system.

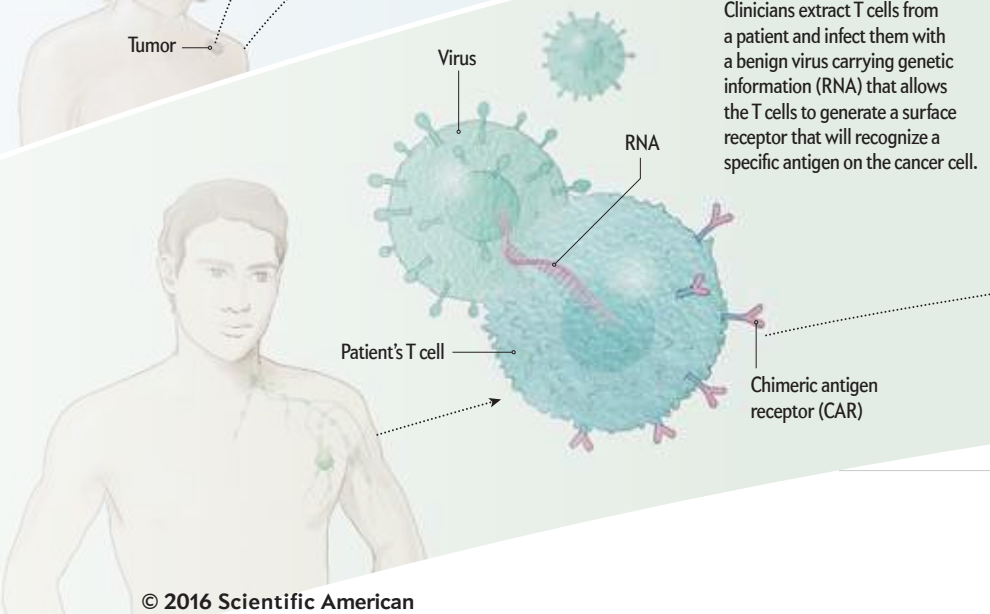
Dendritic Cell Vaccine

Dendritic cells normally patrol the body looking for bits of proteins called antigens that look unfamiliar. They present the offending antigens to other immune defenders, known as CD4+ and CD8+ T cells. The T cells then attack any other cells that bear the targeted antigen. By choosing antigens found on cancer cells but not on healthy ones and mixing the antigens with a patient's own dendritic cells outside the body, researchers create a kind of vaccine that will seek out and destroy those same cancer cells for years to come.


Cancer-specific antigen
Researchers compare the genetic blueprints of malignant and healthy cells, looking for information about antigens that are found only on the cancer cells. These antigens are added to the dendritic cells, which absorb them. The now mature dendritic cells are then reinjected.
Cancer cell
Researchers extract healthy cells, cancer cells and immature dendritic cells from a patient.
Immature dendritic cell
Tumor

CAR-T Cells

Chimeric antigen receptor T cells, or CAR-T, combine attributes of two types of immune defenders: T cells and B cells. Molecules called receptors found on a CAR-T cell look like a hybrid of receptors on B cells and T cells. The CAR protein allows this unusual cell to both latch onto select antigens and destroy any cells that bear the target antigen. This mishmash eliminates intermediate steps typically taken by B and T cells, making CAR-T cells virtually unstoppable.


Clinicians extract T cells from a patient and infect them with a benign virus carrying genetic information (RNA) that allows the T cells to generate a surface receptor that will recognize a specific antigen on the cancer cell.
Virus
RNA
Patient's T cell
Chimeric antigen receptor (CAR)

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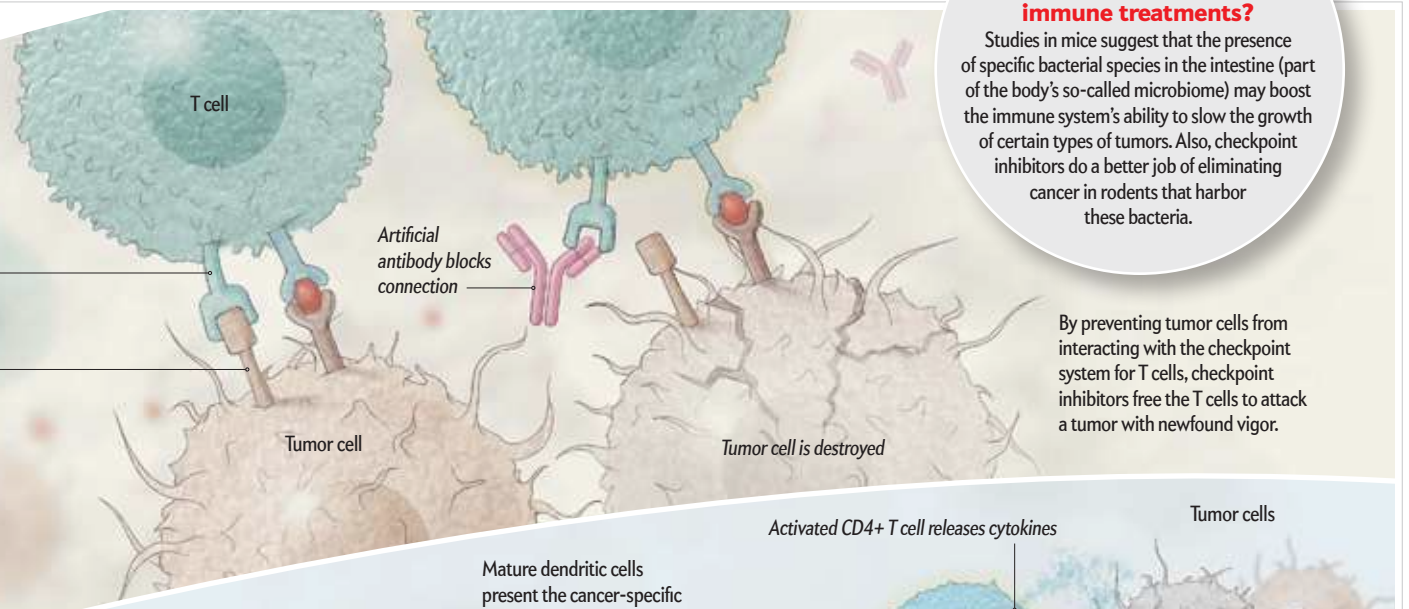
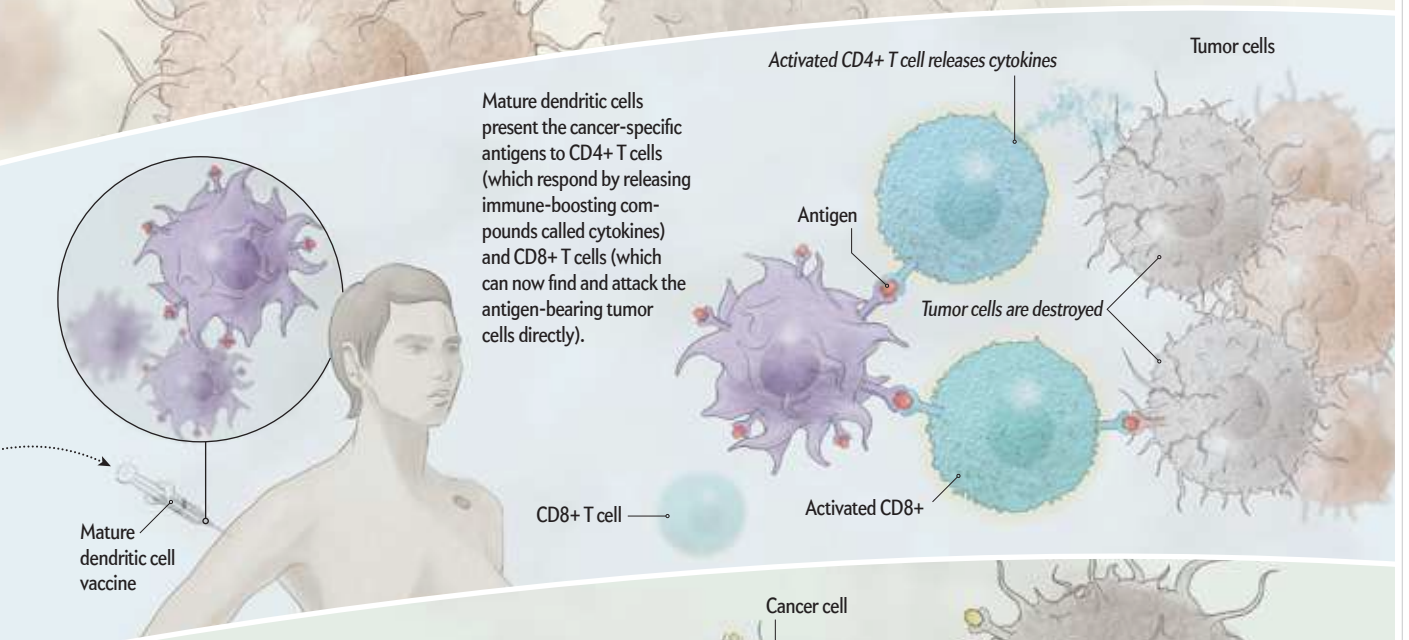
Could intestinal bacteria boost the effectiveness of immune treatments?

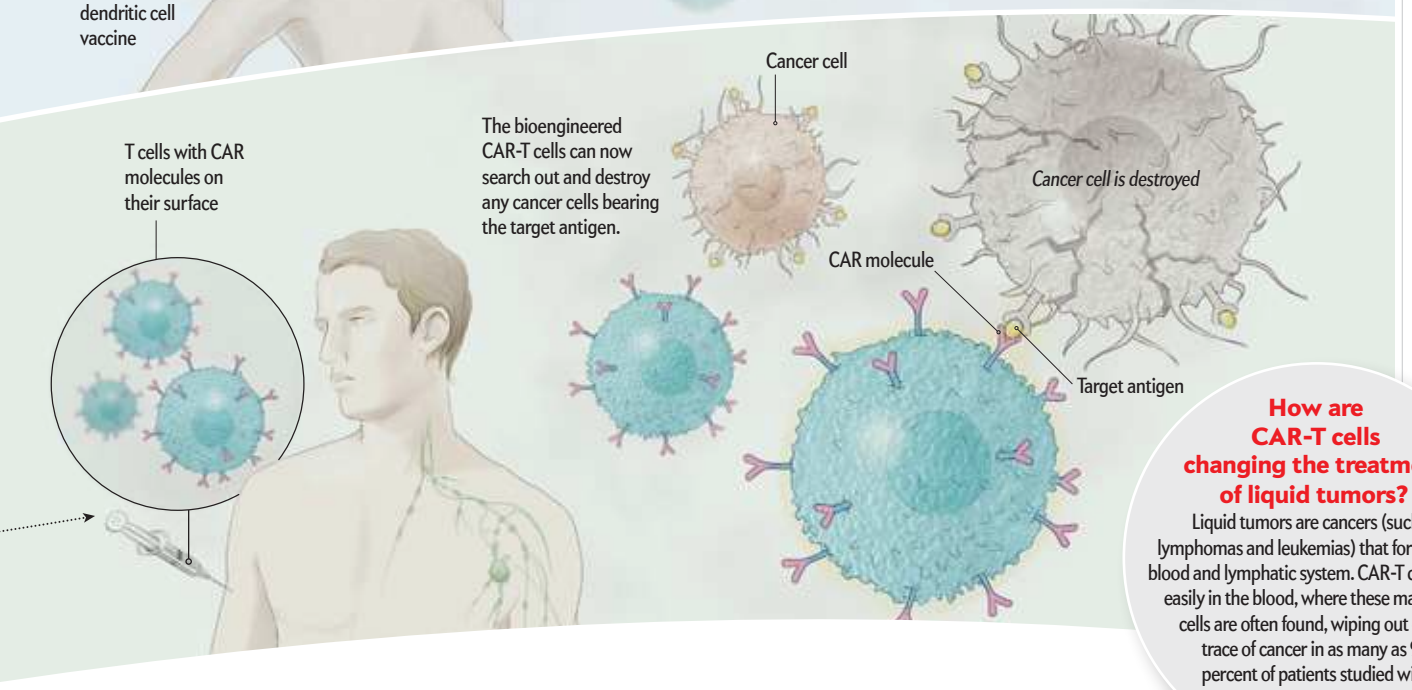
Studies in mice suggest that the presence of specific bacterial species in the intestine (part of the body's so-called microbiome) may boost the immune system's ability to slow the growth of certain types of tumors. Also, checkpoint inhibitors do a better job of eliminating cancer in rodents that harbor these bacteria.



By preventing tumor cells from interacting with the checkpoint system for T cells, checkpoint inhibitors free the T cells to attack a tumor with newfound vigor.



Mature dendritic cells present the cancer-specific antigens to CD4+ T cells (which respond by releasing immune-boosting compounds called cytokines) and CD8+ T cells (which can now find and attack the antigen-bearing tumor cells directly).



The bioengineered CAR-T cells can now search out and destroy any cancer cells bearing the target antigen.

How are CAR-T cells changing the treatment of liquid tumors?

Liquid tumors are cancers (such as lymphomas and leukemias) that form in the blood and lymphatic system. CAR-T cells travel easily in the blood, where these malignant cells are often found, wiping out every trace of cancer in as many as 90 percent of patients studied with an aggressive leukemia.

Illustration by Shizuka N. Aoki

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A Vaccine for Cancer?

Targeting cancer cells using their own DNA could help eliminate tumors and prevent recurrences

By Beatriz M. Carreno and Elaine R. Mardis

For more than a decade researchers have been trying to supercharge human defense systems against cancer with the help of a vaccine. These injections are not designed to prevent cancer from starting. Instead they provide a patient's immune system with intel on what the enemy—cancer cells—looks like. Ordinarily, cancerous cells do not look different enough from normal cells to trigger an immune system response, but we have figured out ways to highlight and target some of the proteins that are unique to these malignancies.

Human cells are covered in so-called self-proteins that serve as identifying markers for the immune system. Like an ID card, they let the body know whether a substance belongs in the body and should not be attacked. Unfortunately, those proteins also dot the exterior of cancerous cells. Earlier cancer vaccine efforts, by our team and others, may have failed because they primed the immune system to look for proteins present—though at different levels—on both.

Recently, however, our team has managed to home in on proteins that are unique to the malignancies by scouring genome sequences of a patient's normal tissue and a tumor to identify proteins exclusive to the cancer. Then we study which cancer-specific proteins spark a strong response from immune molecules charged with directing the body's response to foreign substances, called major histocompatibility complex proteins, or MHCs. Using that information, we can create personalized vaccines that include MHC-containing dendritic cells from the patient that will grab the cancer proteins and present them to the immune system. That stimulus helps to generate antitumor T cell responses and marks cancer cells bearing those specific proteins for destruction.

In 2015 we tried this approach with three melanoma patients. As we wrote in *Science*, we found seven cancer-specific proteins that would bind to each patient's MHC molecules. We were thrilled to see a response in all three subjects: three of the seven proteins were recognized by the patients' T cells, and those T cells attacked the patients' cancer cells.

A year later the patients' immune systems continued producing antitumor T cells in the blood, suggesting that our vaccines could fight off tumor recurrences. (Two of our patients' tumors shrunk or stabilized, but because they received other therapies, too, we do not know what helped.) To date, all three patients are alive and stable and show no negative side effects from the vaccine.

Our work is still in its early days. We first selected melanoma to treat because it is a cancer with many mutations and protein targets, but we plan to test this approach with other cancers, too. Before our method could become part of routine cancer therapy, we would need to study how it affects tumors long term and speed up our vaccine production time. Eventually we would like to use these vaccines to complement other cancer immunotherapies. Ultimately, we hope, vaccines will give patients a better shot against cancer.

Beatriz M. Carreno is an associate professor of pathology and laboratory medicine at the University of Pennsylvania. **Elaine R. Mardis** is Robert E. and Louise F. Dunn Distinguished Professor of Medicine and co-director of the McDonnell Genome Institute at Washington University in St. Louis. Both Carreno and Mardis study how human immunology and cancer genomics may improve therapies directed at cancer.

cells. The clumps of cancer cells have an assortment of malformed proteins on the surface, which T cells are supposed to spot, swarm around and destroy before the aberrant growth has a chance to get any bigger. But every now and then a nascent tumor develops a way to send out chemical signals that tell the T cells that all is well and to stand down their attack.

In effect, the cancer cells have hijacked a normal feature of the immune system: a safety mechanism that tamps down the body's rampaging defense cells before they start damaging healthy tissue. More specifically, this safety mechanism consists of a series of checkpoints, or gateways, that either rally defense cells to attack or turn them off, depending on which chemical signals are present. (If the checkpoints ever got stuck in the "open" position, the ensuing immune reaction would likely kill a person faster than any malignant growth could.) By producing proteins that block the checkpoint system, cancer cells prevent the immune system from ever ramping up to fight off cancer. Blocking that false signal with ipilimumab or other so-called checkpoint inhibitors reawakens the immune cells, allowing them once again to zero in on their targets.

Ipilimumab soon proved effective in lung cancer as well as melanoma, and pharmaceutical companies began developing other drugs that used the same strategy. Former U.S. president Jimmy Carter, at 91, whose melanoma had spread to his brain, took one such drug, pembrolizumab, and he announced late in 2015 that the drug had cleared all his tumors.

Boyer, on a similar regimen with a similar disease, has not fared as well. And that is a puzzle. Some researchers speculate that Carter's advanced age may have helped him. Older cancer cells have more mutations, so his immune system may have needed just a single nudge to release the T cells that were already there. In some patients, though, the T cells may never have made it into the tumor, and so there was nothing there to unblock. In other patients, the T cells seem to be in the right place, but the drug still does not work—perhaps because multiple steps need to be unjammed. A 2015 study in the *New England Journal of Medicine* showed that more melanoma patients did better when given two checkpoint inhibitors instead of one.

Still, doctors are not good at predicting who will respond to which checkpoint inhibitor or combination of treatments, and so Boyer and patients like her have to keep experimenting with different therapies. Today just more than 20 percent of advanced melanoma patients in clinical trials get a complete response from checkpoint inhibitors, with slightly more than half having some

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response. To confuse matters even more, some tumors that appear to attract few T cells still respond to checkpoint inhibitors, whereas the drugs sometimes have no effect on other tumors that contain lots of T cells—suggesting the cancer is playing other tricks.

That has made picking an effective solid tumor treatment for a particular individual a matter of trial and error, as Boyer's experience illustrates. Two years after surgery to remove the cancerous mole from her back, she learned that the melanoma had returned and was spreading throughout her lungs and chest. Because the growths were now too large to be cut out, Boyer agreed with her physicians to take part in a clinical trial at the beginning of 2013 that would inject her with high doses of interleukin-2 (IL-2), one of dozens of different chemical signals that help to boost the immune system's ability to fight cancer. At first the drug seemed to stop the growth of Boyer's tumors, but after three months, scans showed that the cancer was on the move again.

Boyer opted for a second clinical trial, this time pairing the recently approved checkpoint inhibitor ipilimumab with still another immune-signaling molecule known as IL-21. Within a few weeks, however, the side effects of the IL-21 treatment (nausea, diarrhea and unbearable pain) had become so disabling that Boyer had to stop getting the injections, although she continued receiving the ipilimumab. By the end of 2013 some of the cancerous spots had started to expand, and so her medical team opted for radiation to try to limit the growth. By spring of the following year a few of these tumors were smaller, but new ones had appeared on her head and in her breast.

Surgery dispatched the lump in her breast, and two other immune-boosting therapies seemed to hold the rest of her tumors in check for a while. By January 2015, however, it became clear that she needed another plan of action—new spots had begun to grow in her brain, breast and abdomen. A month later she entered a clinical trial, which combined yet another checkpoint inhibitor with a drug that is supposed to slow tumor growth. As this article went to press, Boyer's cancerous spots remain stable.

There is no denying that so many treatments have battered Boyer's body. She spends her nights and many of her days in a plush loveseat to rest her back. She goes to work as a structural engineer most mornings on the weeks she has off from her sixth and current round of treatment. Otherwise she entertains herself by playing video games—Call of Duty is her favorite. All told, however, she does not regret trying six different immunotherapy regimens so far. "It seems to me that some of these treatments maybe slowed down the growth a little bit," she says. One of her doctors, Boyer remembers, "said part of the game for melanoma was not necessarily finding the right treatment now but keeping yourself alive long enough until they find the right treatment." And so she is and so far accepts her current quality of life.

LOOKING AHEAD

BECAUSE BOYER and other patients are living long enough to feel some contentment, Genentech's Mellman is excited. For immunotherapy, possibilities have begun to turn into actual results in patients, he says. Investigators no longer worry about whether their research will eventually help someone; now they can spend their time making effective treatments better. "We need to find the boundaries and limitations and figure out how to get around them," Mellman says, but "this is an incredibly inspiring and thrilling way to do science."

Eventually the process of selecting an immune treatment will become more logical, he believes. A patient with a solid tumor might first have the tumor biopsied to look for the presence of T cells. If enough T cells were in the tumor, the person would likely be given a single checkpoint inhibitor or maybe several inhibitors. (At present, the FDA has approved four checkpoint inhibitors, but more than a dozen others are under development.) If the tumor has not already attracted many T cells, doctors may try various other techniques to both drive the immune cells in and call the immune system's attention to the abnormal growth before opening the checkpoints.

Researchers are also considering how to use standard cancer care, including radiation and chemotherapy, to boost the immune response. Killing a number of tumor cells with lower doses of chemotherapy or radiation should release lots of cellular debris from the tumor, thereby alerting the immune system to send T cells to whatever abnormal growth remains. (Getting the balance right may be tricky because too much chemotherapy and radiation have also been shown to suppress parts of the immune system.) Then, the addition of a checkpoint inhibitor might be able to effectively fight the weakened cancer before it has a chance to recover. But scientists have only just begun to test such hypotheses.

Finally, as more and more immunotherapies are approved by the FDA, they present an entirely different, nonmedical challenge: price. Combining therapies raises the cost of what are already quite expensive treatments. The global market for oncology drugs has now surpassed $100 billion a year, according to IMS Health, a medical data company, but drug firm executives acknowledge that insurers and the public will not be willing or able to indefinitely combine drugs that can run $150,000 or more per patient. They are looking at manufacturing improvements, lower doses and shorter treatment times, among other approaches, to lower the eventual cost of treatment.

Even today's curative therapies are far from perfect. Koehler still has some lingering effects from her treatment. She tires more easily than she used to. "The toughest part now is how far do I push myself," she says. But Koehler is able to golf, hike or snowshoe when the weather permits. Cancer doctors believe immunotherapy will soon allow them to give many more patients similar opportunities to enjoy a new lease on life. SA

Karen Weintraub is a freelance health and science journalist who writes regularly for STAT (www.statnews.com), *USA Today* and the *New York Times*, among others.

MORE TO EXPLORE

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PUBLIC HEALTH

HOW ZIK

IN BRIEF

Zika virus was first detected about 70 years ago in Uganda, and until 2015 it remained under the radar and localized to minor outbreaks.

By spring 2016, the virus went global, including several cases in the U.S. It is spread by the bite of a feeding mosquito or sexual contact and can cause birth defects and other health problems.

Early studies of samples of virus isolated from mosquito saliva have shown that the genetic makeup of the virus has changed very little since it was first identified—signaling that changes in the environment are likely responsible for its recent global explosion.

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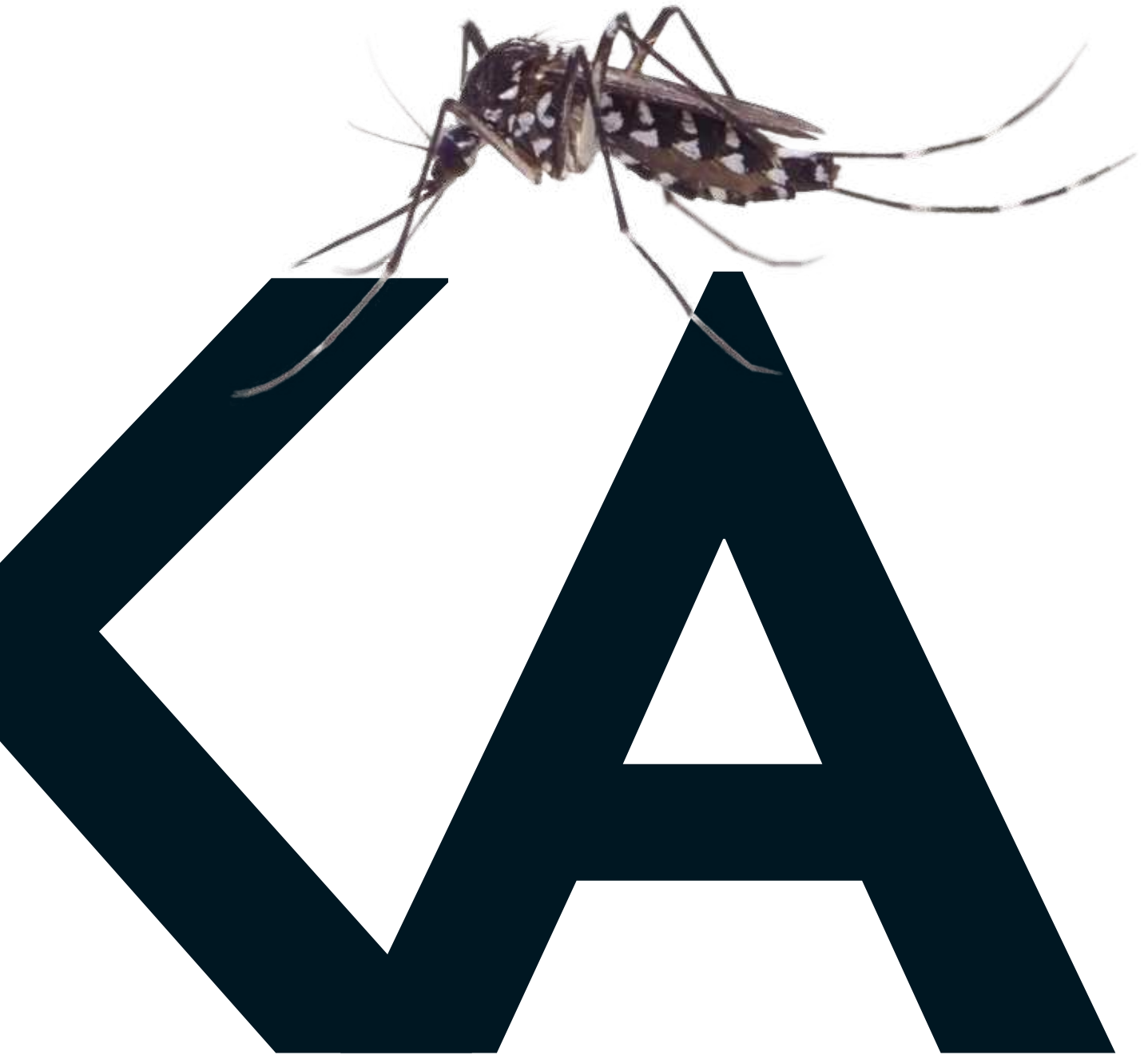

ZIKA SPIRALED OUT OF CONTROL

This spring our reporter went into the lab to see how scientists are gathering clues to Zika's sudden spread around the world

By Dina Fine Maron

GETTY IMAGES

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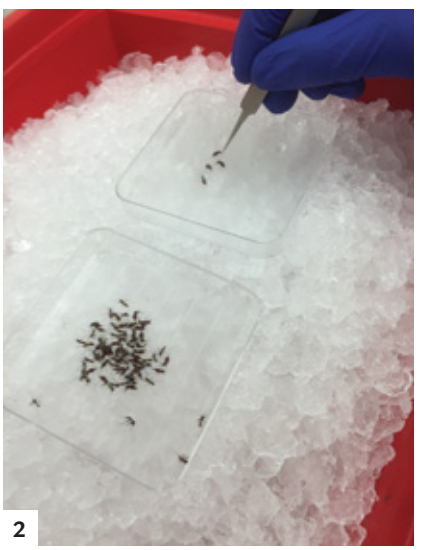
THE WORLD'S BIGGEST COLLECTION OF ZIKA VIRUS IS HOUSED IN A TAN concrete building, rising up from the flat campus of the University of Texas Medical Branch (UTMB) here in Galveston. Inside, armed guards watch the lobby, and access to certain floors requires special clearance. These safeguards are in place because other viruses, including those that cause Ebola and severe acute respiratory syndrome (SARS), are also on the premises.

Zika is not as easily spread as deadly Ebola, so the laboratories that work with the mosquito-carried virus do not require spacesuitlike protection gear. On a recent visit I held a clear plastic bag containing the complete virus collection in my bare hands. Inside the bag the 17 vials of pure, freeze-dried virus resembled old glue. They did not look like the material of a global health crisis that has panicked entire nations. (The scientist who handed me the bag did keep one hand hovering nearby, presumably ready to catch if I dropped it.) Despite its modest appearance, experiments with the collection may be researchers' best hope of understanding how the virus got so out of control—and what to do about it.

1



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THIS PLASTIC BAG holds the world's largest collection of pure Zika virus, housed at the University of Texas Medical Branch at Galveston (*1*). Scientists stun mosquitoes by putting them on ice during Zika virus experiments (*2*).

The virus was first detected in Uganda, and for nearly 70 years it stayed small and scientists took little notice, believing all it did was cause symptoms on par with a mild flu. But since 2015 Zika has ricocheted to over 40 countries, transmitted by mosquito bite or human sexual contact. [*Editor's note: As of September 2016, the number had increased to more than 50.*] Researchers now blame it for terrible birth defects, including microcephaly, when babies are born with abnormally tiny heads, and Guillain-Barré syndrome, an autoimmune disease that can affect patients of any age. "The more we learn, the worse it gets," says Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health.

Virologists now need to figure out which of two potential causes is responsible for the Zika explosion. One possibility is that genetic changes within the virus supercharged its ability to infect people and cause disease. The second scenario is that the change happened outside the virus: after decades of relative isolation, it reached dense population areas, providing more fertile ground for its spread. If researchers identify new mutations within the virus that also allow it to breach the placenta and cause microcephaly in fetuses, then they could be on the lookout for ways to combat that transmission, too.

If the outbreaks are just the result of environmental changes, perhaps Zika was always capable of causing serious effects, but they were rare in small populations and only became obvious when the virus hit a lot of people. "It could just be a numbers game," says Erin Staples, a U.S. Centers for Disease Control and Prevention medical epidemiologist. (There is a third, less accepted theory suggesting that previous exposure to another virus called dengue could somehow make people more

Photographs by Dina Fine Maron

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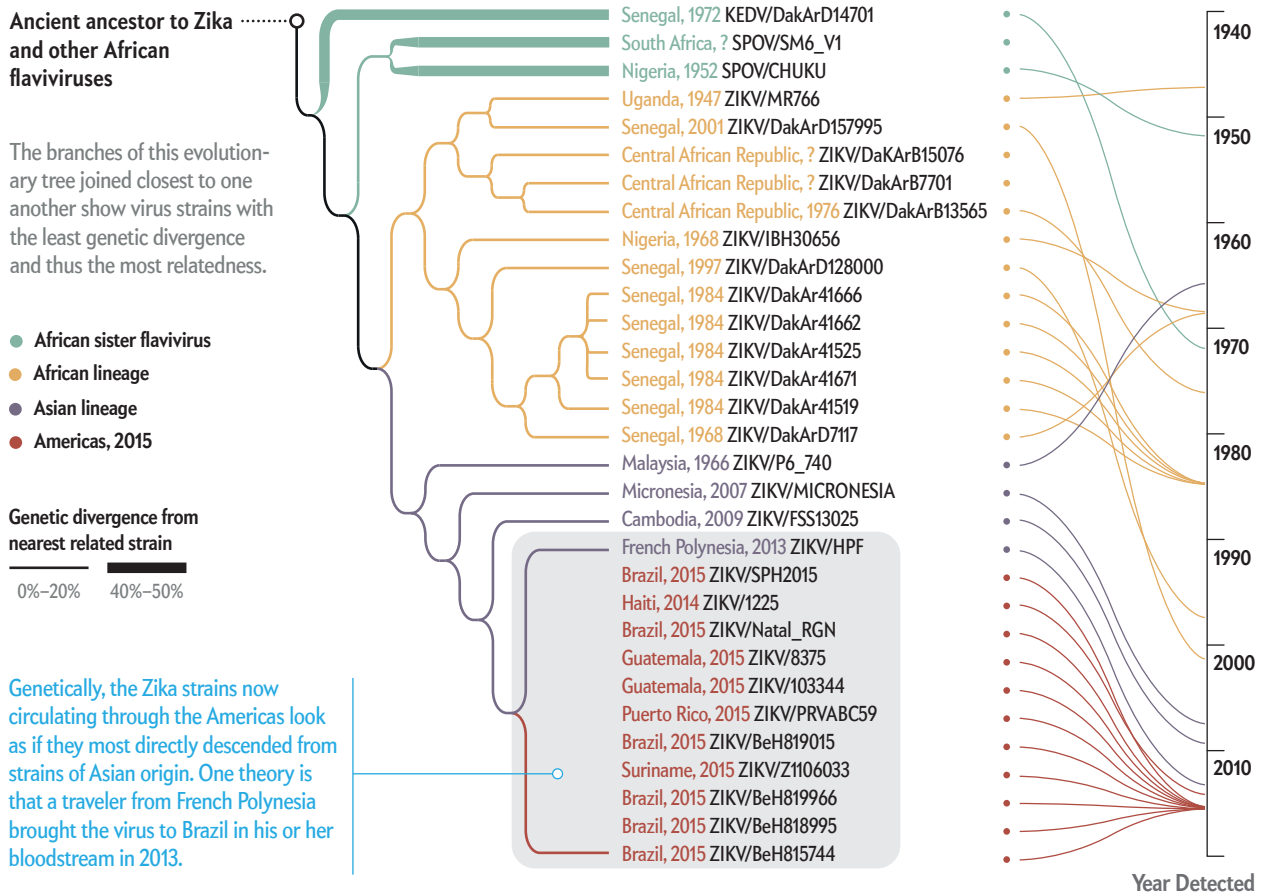
FINDINGS

Zika's Global Connections

Zika has spread to many places around the world (*map*). Even so, there is little difference among the various genetic strains (*below*), according to an analysis by researchers at the University of Texas Medical Branch at Galveston. For example, the strain currently in the Americas and another previously detected in French Polynesia are practically indistinguishable from each other (*group in gray box*).

These findings suggest that mutations probably do not account for the virus's recent spread or for the birth defects, such as microcephaly, that have been reported in many countries in recent years. Instead the virus may be causing havoc now because it has reached more populous places where it can be transmitted rapidly among people who have not been exposed to Zika before. —*D.F.M.*



Editor's note: Since February, infections have also occurred throughout the Caribbean and in the U.S. (Florida).

SOURCES: "ZIKA VIRUS VECTORS AND RESERVOIRS," BY SCOTT C. WEAVER. UNIVERSITY OF TEXAS MEDICAL BRANCH, FEBRUARY 26, 2016; "ZIKA VIRUS OUTSIDE AFRICA," BY EDWARD B. HAYES, IN *EMERGING INFECTIOUS DISEASES*, VOL. 15, NO. 9, SEPTEMBER 2009; CENTERS FOR DISEASE CONTROL AND PREVENTION

Graphic by Tiffany Farrant-Gonzalez

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IN BANGKOK, a city worker sprays chemicals in a school to kill mosquitoes, in hopes of stopping the spread of the Zika virus.

LILLIAN SUWANRUMPHA Getty Images

susceptible to Zika. But there is little support for this compared with the other two ideas.)

Galveston is an ideal place to tackle this inside versus outside debate because the Medical Branch research center is home to the massive World Reference Center for Emerging Viruses and Arboviruses (the latter are viruses carried by ticks, mosquitoes or other arthropods). The collection includes more than 7,000 pathogens. Investigators also have a variety of specialized resources for testing virus infectivity in various bugs and animals, sequencing viral genes and imaging pathogen structures.

SPITTING IMAGE

FOR CHOOSING among competing theories about what went wrong with Zika, it also helps that arbovirus expert Scott Weaver, the university's director of the Institute for Human Infections and Immunity, and his colleagues have become good at a rather arcane skill: making mosquitoes spit.

For the past few months Weaver's team has fed lab-grown mosquitoes—related to the insects spreading disease in Brazil and the Dominican Republic—blood meals spiked with either a 2015 Zika strain from Mexico, a 2010 strain from Cambodia or a 1984 strain from Senegal. The scientists wait a bit, then coax the mosquitoes to spit, and examine that saliva for the amount of Zika virus particles it contains. Comparing mosquitoes that carry different Zika strains lets the researchers test whether newer strains travel more quickly from insects' guts to their saliva than do older strains. Such increased speed in a virus is often caused by a genetic change. If the virus now found in the Americas and Caribbean moves into the bugs' spit faster than other strains do, it could fuel a larger, faster-moving outbreak in humans—and favor the inside version in the inside/outside hypotheses duel.

Doctoral student Christopher Roundy has become the main drool wrangler. "Basically I spend my days collecting mosquito spit," Roundy says. "It doesn't sound that glamorous." He begins the tests in Weaver's lab by mixing a specific strain of Zika with human blood donated by a local hospital. (The blood was getting too old for use in human transfusions.) Next he pours the spiked blood into a metal canister that he covers with skin from a mouse—mosquitoes are more likely to bite through skin. The other side of the canister is hooked to a heater because mosquitoes also prefer warm meals. The whole setup is then placed, skin-side down, over the opening of a small Styrofoam container holding dozens of female mosquitoes (males do not bite). Frenzied by the smell of blood, the females stab their proboscises through the skin, sometimes two or three times. Once they are full, their stomachs become red and engorged—making it clear that they have eaten.

For some, this is their last meal. Every day afterward a small number of those bugs are killed and taken apart. Their bodies, sans legs, are blended into a slurry; the legs are similarly pureed and studied separately. Both batches of bug bits are then

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scrutinized for signs of the virus—indicators of how far the pathogen traveled in the body.

After eight days Roundy turns his attention to the bugs' spit. He stuns a handful of the remaining live mosquitoes by placing them in the freezer for about a minute. Then Roundy uses tweezers and a magnifying glass to gently guide each of their proboscises into a small tube containing a salt solution. That exposure to the salty mix forces them to drool. He adds that spit to dishes of cells and mixes in chemicals that cause Zika-infected cells to turn a purplish color. The purple cells are visible to the naked eye. Under a microscope, Roundy also examines the spit for tiny purple blotches—viral particles—that he might have missed.

If there are genetic changes in newer Zika strains, Roundy, Weaver and UTMB pathologist Nikos Vasilakis are particularly interested in any that might help the virus infiltrate human cells or aid its journey via mosquito bite. They also want to know if mutations may explain its connections to microcephaly. More virus in any single drop of blood, for example—thanks to boosted replication rates of the organism—could perhaps help the virus to more readily cross the placental barrier and reach a developing fetus. If there are no such changes, that is telling, too. It shifts the balance toward the "outside" environmental idea.

Searching for inside/outside evidence using this method has worked before. The same Galveston team used a similar approach to determine that another mosquito-borne disease, chikungunya, had mutated in the past. By studying spit, they found that specific genetic adaptations allowed that virus, normally spread by the *Aedes aegypti* mosquito, to expand its range by jumping to a different carrier, the *Aedes albopictus* mosquito. A single amino acid change in one of the virus's glycoproteins, for example, allowed the virus to replicate about 40 times easier in the bug than it once did. The information prompted health workers to expand warnings about the disease to more areas of the Pacific rather than limiting them to those locations at risk from one of the species. (It is unlikely that Zika made a similar species jump because the virus is already thriving in areas with *A. aegypti,* Weaver says.)

MOVING TARGET

THE ZIKA TEST RESULTS were finalized in late April. After tracking different strains of the virus via thousands of bugs, the Galveston team came to a quiet conclusion: the latest Zika strain does not appear to be more active or more easily transmissible than are prior strains. In fact, older Zika from Africa in the 1980s is a bit quicker traveling through the mosquito body. The discovery does not completely eliminate the idea of harmful genetic changes, yet this evidence tips the scales of blame toward the environment.

For scientists such as Weaver who are concerned about public health, the environmental tilt is disquieting. "It's bad news in a way because that tells us that the strain that is circulating today in Asia and Africa probably has at least the same capacity to initiate urban epidemics," he says. (Immunity in some of those populations from past outbreaks, however, may be protecting them from large epidemics.) The serious symptoms became more apparent as more people grew ill, and public health officials saw enough of an uptick in microcephaly, other birth defects and Guillain-Barré to fuel concern and further investigation.

Kathryn Hanley, a biology professor at New Mexico State University who investigates viruses such as dengue and Zika, notes the environment and internal mutations actually could be working together. "These are not mutually exclusive hypotheses," she says. "It could be that the virus previously had little access to urban populations, but on the way to getting that access it also acquired mutations that increased its transmission." Researchers at Galveston and elsewhere plan further tests on insects and animals to explore this and other ideas.

There are still many unknowns about the virus. For instance, the way Zika infects human cells and hijacks their machinery to copy itself many times has proved elusive. And because this virus looks so much like dengue, testing for Zika has remained a serious challenge, complicating efforts to accurately track the spread. The first large outbreak—in 2007 on Yap Island in Micronesia—infected 70 percent of the island's population but was only identified because scientists had been deployed there on the assumption the isle was under siege by dengue. Other Zika cases have undoubtedly been missed altogether, scientists say.

That suggests researchers have underestimated this virus all along. Perhaps other benign-seeming threats could be more dangerous than previously thought as well, they worry. "You should not necessarily be scared, but you have to be open-minded and quick to respond," says the CDC's Staples. If Zika and other emerging viruses have unexpected effects as they reach different populations, it is a serious problem. Without better global surveillance of diseases in remote locations, health agencies will find it hard to foresee or prepare for an organism that could be quickly transported to an urban area and spiral out of control.

Such surveillance is currently not done: many developing nations have little health infrastructure and few available resources to strengthen it. Moreover, most of the World Health Organization's annual budget comes from donor countries that earmark it for specific projects such as HIV prevention or polio eradication, not surveillance of amorphous threats.

Humanity is not without defenses, however. Some insecticides and larvicides work on the *A. aegypti* mosquito, Zika's preferred host, so disease-control experts know which mosquitoes to study and target. Still, says Ann Powers, a laboratory chief in the CDC's Division of Vector-Borne Diseases, "we need to be more vigilant." All it takes to change the profile of a disease, she knows, is a few extra mosquito bites. SA

Dina Fine Maron is an award-winning journalist and associate editor for health and medicine at *Scientific American.* Maron is also a contributor to the publication's podcasts and Instant Egghead video series. She is based in Washington, D.C.

MORE TO EXPLORE

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LONGEVITY

Living to 120

Drugs we already use for some medical conditions show surprising abilities to keep aging cells healthy. Scientists have new hope that they can develop medicines able to slow aging

By Bill Gifford

In March 2016, officials from *Guinness World Records* traveled to Haifa, Israel, to visit a retired candymaker named Israel Kristal. They came to proclaim him, at the age of 112 years and 178 days, the world's oldest man. Kristal, who has since turned 113, has led an extraordinary life. When he was born, in 1903, life expectancy for a boy in Poland was only about 45 years. As a child, he remembers throwing candies to Emperor Franz Josef of Austria-Hungary. As an adult, he ran a candy factory near Lodz. He lived through two world wars and survived nearly a year in various concentration camps, including a three-month stint at Auschwitz. His wife and two children were killed. After remarrying, he immigrated to Israel, where he made artisanal confections by hand. He now has something like 20 great-grandchildren. Born in the era of gas lamps, the centenarian now lives in the age of Twitter.

"Mr. Kristal's achievement is remarkable," said Marco Frigatti, head of records for Guinness, in an official statement. Indeed, the average life expectancy of a male in the developed world is close to 80 years. Only about two in 10,000 people live to age 100, and the vast majority of centenarians are female. At 113 and change, Kristal is near the limit of maximum observed life span for men. No human being has ever outlived Jeanne Calment of France, who died in 1997 at the age of 122.

What if, instead of dying at 80 or 85, the average person lived to be 100 or even 113 like Kristal? False promises of longer lives, even immortality, date back to the days of the alchemists, of course. So far there has not been much evidence to support such optimism. But some scientists believe centenarians such as Kristal really do age more slowly than the average person. Legitimate findings of current biological research hint that periods of extreme calorie restriction—perhaps like those experienced by the candymaker—affect the life spans of cells. This research is showing more precise ways to stretch those limits, not with diets, but with drugs.

Half a dozen medications or supplements, all of which have already been approved for human use for other purposes, turn out to target mechanisms within our cells that seem to improve internal damage control and thus help to prolong life. Some of these substances, including an anticancer drug, have already been shown to increase average and maximum life span in mice and other laboratory animals. A popular diabetes drug called metformin is headed for the first clinical trial ever designed to reveal whether a medication works to slow aging in people.

IN BRIEF

Diets and other strategies, despite promising results in simple organisms and even mice, have failed to reliably extend healthy life spans in humans and other primates.

Mechanisms within cells triggered by dietary deprivation, however, are proving to be promising life-extension targets.

Drugs, including an antidiabetes medication and an anticancer drug, aim at these mechanisms and are now being tested for antiaging potential.

Photograph by Andrew Myers

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Because of this activity, a small coterie of well-established aging researchers is beginning to say that serious life extension could become a reality within the lifetimes of people reading this magazine. "There's been so much crazy talk about living forever and 'hacking' aging that it kind of drowns out what we know is possible now," says Matt Kaeberlein, a leading biogerontologist at the University of Washington. "The way the research is going, I see maybe 25 to 50 percent increases in healthy longevity as plausible in the next 40 or 50 years."

"There's been a huge response and huge interest and a feeling that something big is going to happen," says Nir Barzilai, a leader of the metformin trial and director of aging research at the Albert Einstein College of Medicine. "I think we'll get significant results. And the next drugs will be better."

BEYOND DIET

AGING, AT LEAST IN PART, is rooted in our appetites. Scientists have known since the 1930s that underfeeding lab animals such as mice and rats can enable them to live longer—in some experiments, as much as 40 percent longer. Even nonscientists like Kristal think that the episodes of hunger in his life, during and after World War II, may have contributed to his longevity. In an interview with the newspaper *Haaretz,* he said, "I eat to live, and I don't live to eat. You don't need too much. Anything that's too much isn't good."

Unfortunately—or fortunately, depending on one's point of view—experiments with extreme caloric restriction in monkeys, animals more similar to people, have had mixed results. Low calorie consumption seemed to work well in one study, but then another well-designed trial showed that simply eating a more natural, whole-foods based diet, with a low sugar content, seemed to help just as much, regardless of calorie count. And in any event, very few humans can stick to a diet that requires cutting calories by 25 percent.

But experiments in lower organisms have revealed specific, beneficial cellular pathways—chains of molecular interactions—that are triggered when nutrients are scarce. These pathways evolved to allow organisms to survive long periods without food. In theory, activating such pathways with drugs could yield the same benefit without the pain of starving oneself. One example involves the enzyme AMPK, which acts as a kind of cellular fuel gauge. When nutrients are low, as happens during intense exercise or caloric restriction, AMPK jumps into action, transporting glucose into cells for energy and increasing cells' sensitivity to hormones that aid in this transport, such as insulin. It also helps break down fat for more energy. During exercise, AMPK stimulates the creation of new mitochondria, the energy producers within cells. All of these things improve health.

There is compelling evidence that aging and the rate of metabolism—the process by which a body converts food to energy—are directly linked. In 1993 Cynthia Kenyon of the University of California, San Francisco, discovered that mutations in just one specific gene called *DAF-2* could double the life span of the *Caenorhabditis elegans* worm. That gene is also linked to metabolic rates. But scientists still know relatively little about the genetics of aging, so for now their preferred targets are the higher-level mechanics of the cell.

One of the most promising antiaging mechanisms was discovered by accident. In 2001 biologist Valter Longo of the University of Southern California went away for a weekend and forgot to feed yeast cells that he was using in an experiment. He was surprised to discover that starving them completely for a time made them live longer than usual. The reason, he learned, lay in a cascade of molecular actions usually referred to by the enzyme at its center, which is called mTOR.

This pathway was originally discovered years earlier thanks to a drug called rapamycin, which was found in soil bacteria. The drug, scientists learned, affected a major pathway regulating growth and division in the cell, like the circuit breaker in a tiny factory. Researchers named the path mTOR because it is a "mechanistic target of rapamycin." When mTOR is activated, the "factory" (that is, the cell) is humming along, producing new proteins, growing and ultimately dividing. When mTOR is blocked, such as by rapamycin—or by short-term fasting—cell growth and replication slow down or stop. This is why rapamycin has been effective as an immunosuppressor to protect transplanted organs and more recently as a cancer therapy; these conditions involve runaway cell division.

Longo's work led to the revelation of mTOR's crucial role in aging. When nutrients are scarce, mTOR is inhibited, and the factory goes into a more efficient mode, recycling old proteins to make new ones, ramping up the production of cellular cleaning and repair mechanisms, and hunkering down to wait out the famine. Cell division slows down. And the animal is better able to survive until its next meal.

"What mTOR really does is, it senses the environment, and if there's lots of food around, then it gets cranked up—and in simple organisms, it causes them to develop really quickly and reproduce," Kaeberlein explains. "That makes a lot of sense because when there's lots of food, that's a really good time to make babies." No wonder the mTOR mechanism has been such a big evolutionary hit, used and reused by creatures up and down the tree of life, from single-celled yeast all the way up to humans and whales.

The activity change affects survival. In 2009 a team of scientists reported in *Nature* that rapamycin made lab mice live longer. This was a stunning finding: No other drug had ever lengthened the life span of mammals in this way in a controlled experiment. And this was not just one group of mice but *three* sets of genetically heterogeneous animals. All groups lived longer and not only on average: the animals' *maximum* life span was lengthened, which some considered clear evidence that the drug was slowing the aging process itself.

The mice given rapamycin generally seemed to stay healthier and more youthful for longer than rodents that did not get the drug. Their tendons, for example, stayed more flexible and elastic. So did their hearts and blood vessels. Even their livers were in better shape than the control mice's. They remained more active, even as they got older. What is more, rapamycin extended average and maximum life span even though mice only got it starting at the age of 20 months. It was like giving 70-year-old women a pill that let them live past 95. Or to put it another way, imagine a drug that would let Kristal live into his 130s.

Other labs were able to reproduce the results and to extend them. Mice given rapamycin throughout their adult lives ended up living 25 percent longer—about the same as if they had been calorically restricted. Mice are not people, of course, but rapamycin raised the possibility, at least, that *something* might slow aging and delay the onset of age-related diseases. "Rapamycin was the first robust hit, the first drug that everybody said that this

PAGE 58: PROP STYLING BY ANGELA CAMPOS *Stockland Martel*

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CELL BIOLOGY

Aging's Off-Switch

In the soil of Easter Island in the 1970s, researchers found a compound that stopped the growth of fungus cells. They called the substance rapamycin after Rapa Nui, the native name for the island. What the compound did, scientists eventually learned, was interfere with an enzyme within cells that is essential for such activities as growth and replication. Because these activities eventually degrade cell functions, blocking the enzyme stretched out the prime of cellular lives. The enzyme, dubbed mTOR for "mechanistic target of rapamycin," seems to be a switch to turn aging off and on in cells and to make animals live longer.

When TOR Is On

The enzyme has two complexes, and the one called mTORC1 acts like a sensor for the cell's environment. When nutrients are abundant and energy for growth is easy to find, mTORC1 kicks the cell into high gear. It helps the cell take up glucose for energy, growth factors that trigger replication, and amino acids that can be used to make proteins essential to all of this labor.

When TOR Is Off

The drug rapamycin shields mTORC1, keeping it from detecting glucose or growth signals or nutrients, even when they surround the cell. As a result, the cell behaves as if it is living through a time of scarcity and slows down to conserve its resources. Major cellular functions are ramped down, in particular growth and replication.

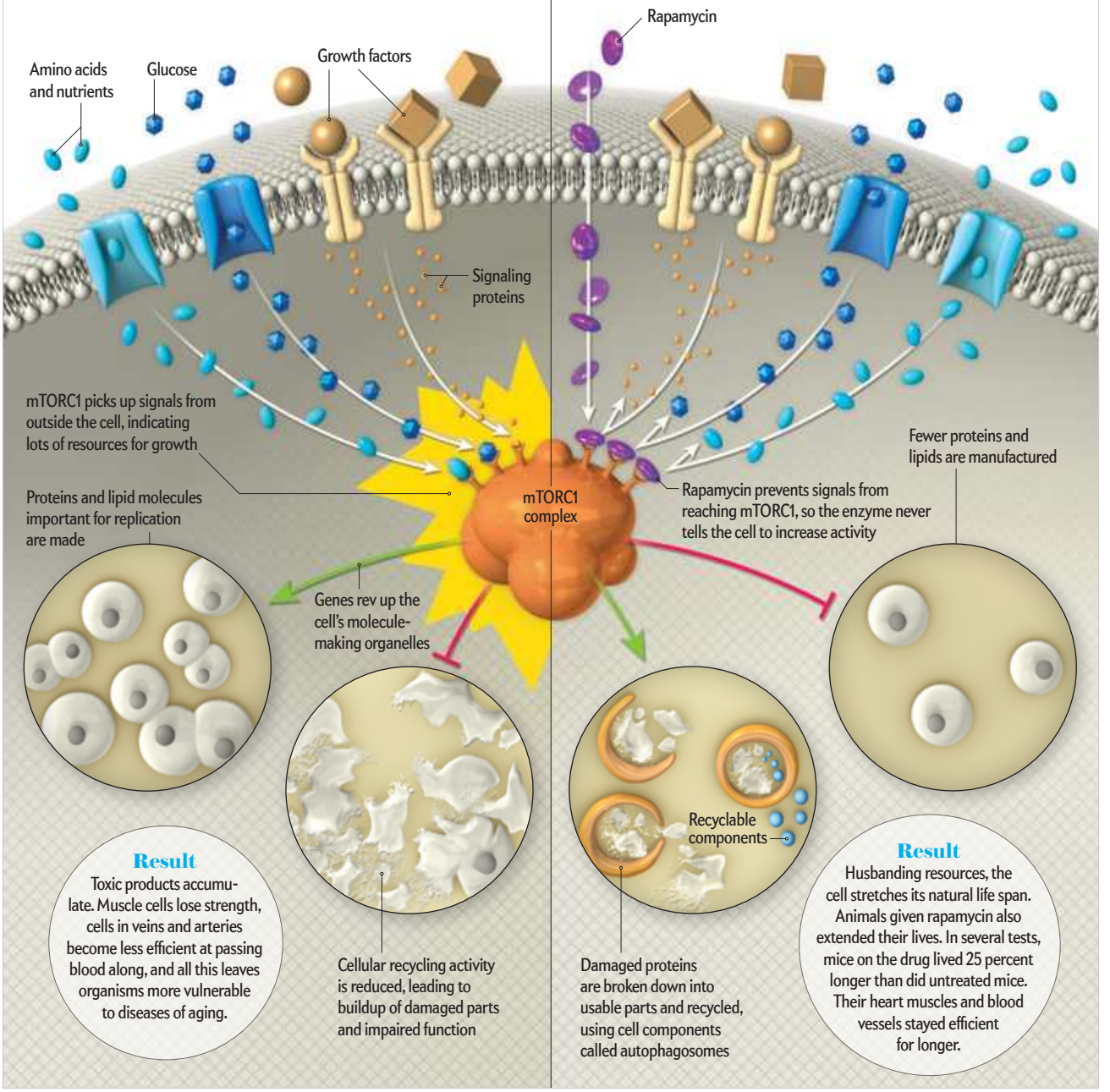
Rapamycin
Amino acids and nutrients
Glucose
Growth factors
Signaling proteins
mTORC1 picks up signals from outside the cell, indicating lots of resources for growth
Proteins and lipid molecules important for replication are made
mTORC1 complex
Rapamycin prevents signals from reaching mTORC1, so the enzyme never tells the cell to increase activity
Fewer proteins and lipids are manufactured
Genes rev up the cell's molecule-making organelles
Recyclable components
Result
Toxic products accumulate. Muscle cells lose strength, cells in veins and arteries become less efficient at passing blood along, and all this leaves organisms more vulnerable to diseases of aging.
Cellular recycling activity is reduced, leading to buildup of damaged parts and impaired function
Damaged proteins are broken down into usable parts and recycled, using cell components called autophagosomes
Result
Husbanding resources, the cell stretches its natural life span. Animals given rapamycin also extended their lives. In several tests, mice on the drug lived 25 percent longer than did untreated mice. Their heart muscles and blood vessels stayed efficient for longer.

Illustration by Emily Cooper

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might be the real thing," says Brian Kennedy, CEO of the Buck Institute for Research on Aging in Novato, Calif.

Rapamycin is not without drawbacks, however. It can have unpleasant side effects, notably the appearance of mouth sores in some patients, and more frequent infections (because it suppresses immune response). In the mouse studies, the males appeared to suffer from testicular shrinkage. Those effects were acceptable for cancer and transplant patients, who were already quite sick, but they might disqualify it as an antiaging drug for otherwise healthy people. But what if you gave it to those healthy people in a different way or in lower doses? Could it, somehow, extend human life span as well?

To try and answer those questions, Kaeberlein and his colleague Daniel Promislow are starting an unusual clinical trial of low-dose rapamycin in middle-aged pet dogs. Our canine companions, they figure, are reasonable stand-ins for us: "They share our environment, and they get all the same diseases we get as they get older," Kaeberlein says. According to their preliminary data, dogs treated with rapamycin for just a few weeks displayed more youthful cardiac function, as measured by an echocardiogram. "We can clearly see that the heart is contracting better in the dogs that have gotten rapamycin than in the ones that haven't," Kaeberlein says. "In aging animals, poor blood flow is probably a factor in the decline of other body tissues."

One encouraging sign for the drug's potential as an antiaging agent, Kaeberlein says, is that in small amounts rapamycin may be working more as an immune modulator rather than a suppressor. It actually appears to *enhance* some kinds of immune function at these lower doses. A small human trial by Novartis, which markets a version of rapamycin as a cancer treatment called Afinitor, showed that older adults who took the drug actually responded better to a flu vaccine. This would indicate that it might enhance the immune response in some cases. One other interesting piece of evidence: a Dutch study found that healthy nonagenarians had lower levels of mTOR activity.

The next step, funds permitting, is to do a longer-term longitudinal study of rapamycin in older dogs, tracking their progress as they age. If the results reflect those achieved in mice—if the dogs live longer and healthier lives—they could justify a human clinical trial. "We could know, five years from now, to what extent it is actually working," Kaeberlein says.

STRETCHING LIVES

CONNECTING "HEALTHIER" to "longer" is key. Our life spans have been stretching out, but the latter part of our lives is prone to periods of disease and disability. As demographers James W. Vaupel and Jim Oeppen demonstrated in a 2002 *Science* paper, life expectancy for the longest-lived populations has been growing more or less linearly since the 1840s (currently Japanese females are at the top of the list). People have been living longer than ever before in human history.

At the same time, however, health span—defined as the length of healthy life—has not been growing quite as fast. This means that the period of disease and disability at the end of life, the dreaded decline of old age, has actually been getting longer. The only thing that changes, as we live longer and longer, is that we fall victim to different ailments. As mortality rates from heart disease and cancer drop, more of us become vulnerable to Alzheimer's disease. One in nine Americans older than 65 is affected by Alzheimer's or other forms of cognitive decline, with risk rising drastically after age 80.

"The rise of Alzheimer's disease has been astonishing, but it's exactly what you would expect if you push people into age windows where this disease is common, the late 70s and 80s," says S. Jay Olshansky, a demographer at the University of Illinois at Chicago. "If we continue on this path, I think that it will get worse. The alternative is to slow aging and compress morbidity and mortality into a shorter time period."

Olshansky has not met Kristal, but the Guinness record holder seems to be the kind of old person he has in mind. At 113, Kristal is still sharp mentally and a witty conversationalist. He has managed to resist the deadly illnesses of aging—not only cancer and heart disease but also Alzheimer's and diabetes, which together account for about half of deaths in the developed world. In centenarians like him, researchers find, the period of sickness at the end of life is often much shorter than for people who die in their 70s. A successful antiaging drug would need to mimic the same effect, rather than merely prolong life at the expense of health and well-being, Olshansky says.

But until very recently, investigators have faced a formidable stumbling block to developing that kind of drug: the U.S. Food and Drug Administration has not considered aging to be a disease. Therefore, it would not approve any drug that targeted the aging process itself. From the agency's point of view, this policy made sense: There is no objective way to "measure" aging—no blood test, for example, that can determine whether a person is aging more quickly or slowly than normal. So how would we know if an antiaging drug was working? That official stance eliminated any incentive for a drug company to invest in research into aging and drugs that might slow it down. There was simply no path to approval and to market.

The path began to clear in 2015, however, when the agency gave approval to a clinical trial meant to assess the antiaging properties of metformin. Approved for type 2 diabetes (the most common form) in the U.K. in the 1950s, metformin passed FDA review in the U.S. in 1994. It has since been prescribed to millions of patients as a first-line treatment. Now available as a cheap generic, it is one of the world's most common prescriptions, so much so that the World Health Organization has declared it an "essential" medication. It increases cells' sensitivity to insulin, the hormone that signals them to take in sugar (glucose) from the blood.

Because so many people take the drug, researchers have been able to detect intriguing patterns among patients. In particular, epidemiological studies have found that those on metformin seem to have a lower incidence of cancer. Other studies have suggested that metformin may have beneficial cardiovascular effects. Moreover, whereas diabetics generally lose several years of life expectancy, a 2014 analysis of British patient data found that older diabetics who were taking metformin were actually living 18 percent *longer* than matched nondiabetic controls. They also lived longer than diabetics using another common class of medications, the sulfonylureas, indicating that it was the metformin itself, and not just control of diabetes, that conferred a longevity advantage.

How exactly that works is not entirely clear. The mechanism of action of metformin, which is derived from an ancient herbal remedy called French lilac or goat's rue, has been debated among scientists for decades. One thing it is known to do is activate the AMPK pathway and its favorable metabolic changes. It also

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seems to affect insulin through other paths and even to inhibit mTOR somewhat.

The possibility that metformin might enhance longevity caught the attention of Albert Einstein's Barzilai, among others. As head of a major study of Ashkenazi Jewish centenarians, Barzilai knew that long-lived people rarely have problems with high blood glucose or diabetes; ultraefficient processing of blood glucose in fact is a marker for longevity. Metformin, he thinks, might alter our metabolism to more closely resemble that of a centenarian. "A lot of its antidiabetic activity is also antiaging, just improving cellular function and insulin sensitivity," Barzilai says. He actually takes the drug himself as a preventive because his parents both had diabetes. He stops just short of saying that everyone older than 50 should think about getting a prescription (he is 60). "It looks like a superdrug," Barzilai says. "It looks like it's involved in many things related to aging."

"There are 60 years of data in humans showing that it targets a whole lot of conditions that, in aggregate, would have you believe that it's targeting fundamental aging processes," agrees James L. Kirkland, director of the Robert and Arlene Kogod Center for Aging Research at the Mayo Clinic and a collaborator on the metformin studies.

Yet to test suspected antiaging drugs in people, researchers have to deal with another obstacle: time. A conventional life span study would require decades to complete—literally, a lifetime. The trial approved in 2015, called TAME, for Targeting Aging with Metformin, takes a different approach. Rather than simply comparing longevity in healthy subjects who get the drug with those who do not, the scientists will instead look at the progression of aging-related diseases in each subject.

One of the hallmarks of aging is the way that older people often develop more than one chronic condition, such as high blood pressure and diabetes or heart disease and cognitive impairment. These so-called comorbidities, one disease on top of another, are a major cause of misery in the elderly (not to mention a driver of increased health care spending). In the TAME trial, scientists plan to give metformin to elderly patients who already have one aging-related condition, such as diabetes or high blood pressure. The subjects will be monitored for five to seven years and compared against a control group that has agreed not to take the drug to see whether or not they go on to acquire other age-related diseases at a faster or slower rate. If metformin is really slowing the aging process, then it should be able to stave off the progression of comorbidities.

The TAME trial, then, will really be measuring metformin's effect on health span—evaluating it as, in essence, preventive medicine. "The same kind of process occurred with, for example, giving antihypertensives to people who haven't had a heart attack," Kirkland says.

If the TAME study is successful, and the drug agency shows an openness to test new medications that target aging, Barzilai thinks, pharmaceutical companies will begin to move into the space—and not just traditional pharma but ventures such as the Google-backed Calico project, where none other than Kenyon, who discovered the *DAF-2* aging gene two decades ago, is vice president of aging research. Calico, some reports have speculated, may be investing more than $1 billion in a search for drugs that will extend health span, an amount close to the entire budget of the National Institute on Aging.

"If longevity is a side effect" of extending health span, Barzilai says half-jokingly, "we'll apologize for that."

PILLS FOR THE AGES

THE PIPELINE of potential antiaging medications is already beginning to fill. Acarbose, another antidiabetic agent, has extended life span significantly in male mice, for example. Like metformin, it is already approved for human use, so it, too, could be a candidate for a clinical trial against aging. Still another drug, alpha-estradiol, has also had good results in the same kind of trials that revealed rapamycin's antiaging effect.

A newer and perhaps even more promising group of antiaging drug candidates does not work on metabolic pathways but by clearing out so-called senescent cells, which have stopped dividing but have not actually died. Like cellular zombies, they sit there and secrete small proteins known as cytokines that can damage the cells around them. Kirkland believes that their true function is as a cancer defense mechanism—a way for the body to kill neighboring cells that may be malignant. Senescent cells also play a role in wound healing because the cytokines they secrete help to marshal the immune system. Unfortunately, their toxic effects reach far beyond the immediate neighborhood, contributing to the low-grade inflammation that characterizes aging bodies—and, paradoxically, increasing cancer risk in surrounding tissues. Kirkland and others see them as a key driver of the aging process.

Even worse, the older we get, the more senescent cells we harbor. What if we could get rid of them? Kirkland and his colleagues, including biologist Jan van Deursen of the Mayo Clinic, have shown that eliminating senescent cells from genetically modified mice seems to increase their health span. The problem is that those cells are very hard to isolate—they are dispersed among healthy cells—and even harder to kill. "They're very resistant to dying," Kirkland says. "They're hardy as all get-out."

A team of researchers at Mayo, the Scripps Research Institute and other institutions looked for drugs that could kill senescent cells by inducing apoptosis, or cell suicide. In 2015 they reported that they had found three. After a short treatment with the drugs, researchers saw a dramatic effect in mice that had high numbers of senescent cells. "That gives us reassurance that it's actually clearing senescent cells. And once they're dead, they're dead."

They have to die, perhaps, so that we might live. SA

Bill Gifford is author of *Spring Chicken: Stay Young Forever (Or Die Trying)* (Grand Central, 2015), a book about the science of aging.

MORE TO EXPLORE

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BIOTECHNOLOGY

THE RED LINE

Scientists are on the threshold of crossing a sharp ethical line: permanently altering the human genetic code

By Stephen S. Hall

Kyle Orwig has been itching to do an experiment that would, in his words, "piss people off." Orwig, a professor at the University of Pittsburgh, is an expert on the intricate biology of sperm cells—in particular, how specialized "stem" cells located in the male testes produce sperm. Every so often, however, a genetic flaw prevents these stem cells from completing this process, thus rendering the male infertile. The experiment Orwig has in mind is to use gene-editing technology to fix this flaw in the sperm-forming stem cells and then transplant them back into infertile mice, thereby demonstrating a potential treatment for male infertility.

It sounds simple enough, and, according to Orwig, it would be relatively straightforward to try—indeed, he has been transplanting sperm-forming stem cells into mice for 20 years. The consequences, however, could be momentous. The kind of experiment Orwig is contemplating would, if successful, push society right up to the brightest red line in contemporary biology: altering the genetic text of the human species in a way that is passed down to future generations.

If shown to be safe, effective and ethically acceptable, germline modification would confer unprecedented power on scientists—the power to edit the susceptibility to disease out of our species' DNA, for example, but also the power to manipulate human inheritance and "improve" the species, an aim that darkly harkens back to the eugenics movement of the early 20th century that reached its nadir in Nazi Germany.

Orwig, a broad-shouldered, burr-headed Oregonian who seems genial and determined, has no intention of crossing ethical lines. But he is something of a provocateur. By demonstrating that infertility in mice could be cured with a modest amount of genetic tinkering, he hopes to trigger a wider awareness that editing human genes is not an abstract, long-term technical challenge, as some have suggested, but a near-term possibility with practical medical consequences. Which is why Orwig recently told a colleague, "Let's just do this and piss some people off. Show them that it's possible, so nobody can say it's impossible. And get people talking about it."

The issue of germ-line modification has assumed great urgency in the past two years because of a powerful gene-editing tool called CRISPR/Cas9, which allows scientists to alter the DNA of any organism—including, potentially, humans—with unprecedented precision and ease. In April 2015 Chinese researchers reported the first attempt to edit the genes of human embryos. The headlines—"Embryo Editing Sparks Epic Debate," in *Nature;* "Eugenics Lurk in the Shadow of CRISPR," in *Science*—signaled broad social unease. In the alarmist shorthand of media accounts, the possibility of gene editing triggered fears of "designer babies" and "genetic enhancement."

The humble sperm cell, however, is a less controversial target. And whereas editing genes in an embryo remains a big challenge, many experts believe that approaching germ-line modifi-

IN BRIEF

New gene-editing techniques may soon be used in treatments for male infertility that involve altering the genetic code of sperm cells. Such alterations would be passed down to future generations, constituting a permanent change in the human genome.

Scientists seeking to quell the public's fears that such a step would cross an ethical red line have argued that the technology is not yet feasible, but others believe the line will be crossed soon.

The demand for infertility treatments has for decades fueled the clinical adoption of new biotechnology, for better and for worse.

Photograph by Andrew Myers

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cation upstream of the embryo, in the sex cells that merge to form a zygote, is easier and arguably safer. Once you modify these cells, however, you are essentially modifying the human genome because the changes are permanently inscribed in the genetic text of the embryos they create. Orwig is among a handful of biologists who have experience genetically modifying and transplanting spermatogonial stem cells, the testicular cells that churn out sperm.

The field of reproductive medicine has a well-established track record for pushing headlong into the clinic with technological innovations. Infertility is also big business. If Orwig were to demonstrate in animals that a simple genetic fix is possible, it would be a tempting procedure for the tens of thousands of men who cannot make their own sperm, for whom options are currently limited, as well as for the in vitro fertilization (IVF) industry, which did an estimated $2 billion in business in 2015 in the U.S. (and perhaps 10 times that amount worldwide).

Before administering any treatment, there must be proof that it works and causes no undue harm. Scientists would require such proof before even contemplating creating a human being with edited genes. Animal versions of those experiments are already under way, however, and the red line may be crossed soon. It could happen in China, where researchers have already taken the first tentative steps in editing human (albeit nonviable) embryos. It could happen in the U.K., where the government has legalized a form of germ-line modification known as mitochondrial replacement therapy and, in February 2016, approved gene-editing experiments on human embryos. And it could happen in an IVF clinic anywhere, building on recipes developed in laboratories such as Orwig's.

"This isn't theoretical," Orwig says. "The mouse is here, and the human is not too far in the future. The pieces are already in place."

KEEP CALM AND CARRY ON

THE CURRENT DEBATE over germ-line modification may feel familiar, but it treads on fundamentally new ground. Scientists began to acquire the Promethean ability to rewrite the language of heredity in the early 1970s, when biologists discovered that they could crudely cut and paste DNA with the use of enzymes harvested from bacteria, a technique called recombinant DNA. That advance caused unease about dangerous, genetically engineered microbes escaping the lab, prompting a voluntary—and unprecedented—moratorium on recombinant DNA research in 1974 and a historic meeting in 1975 of scientists at the Asilomar conference in California. Prominent molecular biologists such as David Baltimore, then at the Massachusetts Institute of Technology, debated the safety of the new technology, which led to federal guidelines governing the research. The Asilomar meeting was correctly viewed as a watershed cultural moment: Michael Rogers published a richly detailed account of "The Pandora's Box Congress" in *Rolling Stone,* and by the time the guidelines were in place, biotechnology emerged as one of the transformative industries of the 20th century.

Although society applauded the scientific community's decision in 1974 to hit the pause button on the headlong rush of research, many scientists felt it was an overreaction to hypothetical safety concerns. James D. Watson, co-discoverer of the DNA double-helix structure, called it "senseless hysteria."

Since Asilomar, controversial biology has often landed in the public square with a bang, prompting big meetings with messy background noise. When the National Academy of Sciences debated recombinant DNA in 1977, protesters opposed to genetic engineering unfurled a banner quoting Adolf Hitler: "We Will Create the Perfect Race." A meeting on human cloning in 2001 became a media circus. Maverick IVF doctors vowed to clone human babies. Television crews followed the would-be cloners everywhere (including to the bathroom). *Wired* magazine, in 2001, proclaimed on its cover: "Someone Will Clone a Human in the Next 12 Months."

This time around there is palpable unease among scientists, but they are also wary that another self-imposed moratorium might hold up progress. The result? Another meeting. In December 2015 the National Academy of Sciences and the National Academy of Medicine co-hosted an international "summit" in Washington, D.C. (with the Royal Society and the Chinese Academy of Sciences). Baltimore acknowledged that altering human inheritance had remained "unthinkable" because of the cumbersome and inefficient first-generation tools of genetic engineering. "Over the years, however, the unthinkable has become conceivable," he said, "and today we sense that we are close to being able to alter human heredity." The overriding question, Baltimore continued, is, "How, if at all, do we as a society want to use this capability?"

The answer, to anyone who sat through the three-day meeting, as I did, seemed to be: we're not sure, but there's plenty of time to think it through. Numerous talks, including a plenary address by genome scientist Eric Lander of the Broad Institute of M.I.T. and Harvard University, stressed the technical hurdles and the lack of compelling medical needs for human germ-line modification in the near future. "It might, might, might be a good idea that before we make permanent changes to the human gene pool," Lander warned, "we should exercise considerable caution."

The organizers deftly steered clear of an Asilomar-like moratorium. Baltimore read a carefully worded statement from the meeting organizers acknowledging that it would be "irresponsible" to pursue human germ-line editing in the clinic at this time. At the close of the summit, he went on to explain that the organizers had deliberately avoided calling for a ban or moratorium. "Neither word did we want to use," he said. "Neither word have we used." Basic research could, and should, proceed unimpeded, but the public need not be concerned about imminent developments: human applications of germ-line editing were implausible, unnecessary, unwise and certainly not right around the corner.

That is not the way everyone in the scientific community sees it. The organizers of the Washington meeting framed the issue as "when, if at all." But a different word often crops up in private conversations with biologists when you ask about the prospects for germ-line editing. That word is "inevitable."

THE TIMELINE

SOME SCIENTISTS viewed the National Academies meeting as an effort to "reinforce the status quo," according to biologist George Church of Harvard Medical School. "They basically want the public to calm down," he says. "That was their goal. And no matter what we said, that was going to be the goal. I don't want to stir [the public] up, and I don't want to calm them down, either. I want them to have an accurate view of where things are going." And the public needs to start thinking about gene editing the human genome now, Church says, be-

PRECEDING PAGE: PROP STYLING BY ANGELA CAMPOS *Stockland Martel*

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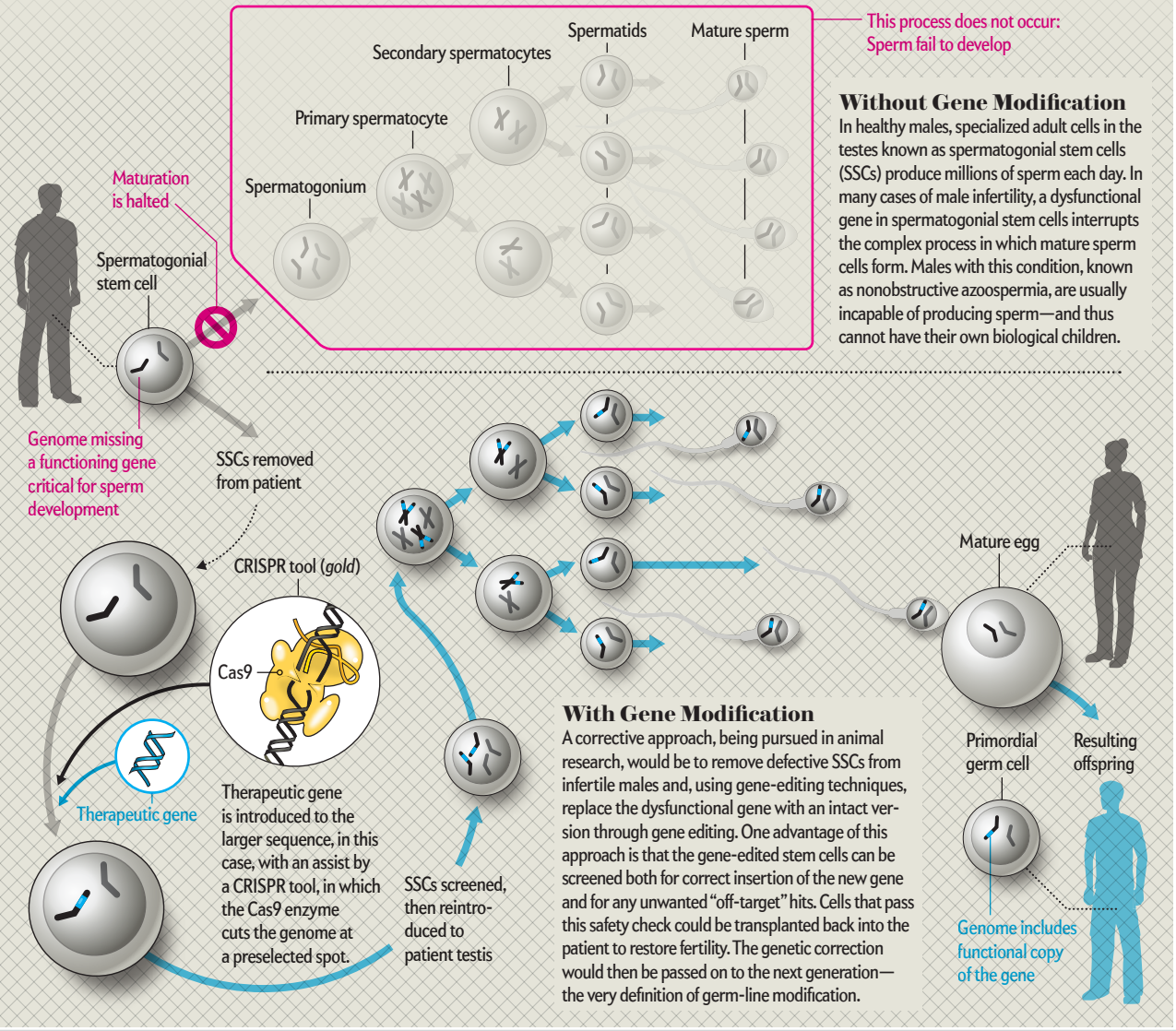
GERM-CELL GENE EDITING

How to Modify the Germ Line

Scientists in China have reportedly tried to edit the genes of human embryos for research purposes. They are also exploring the possibility of modifying genes in sex cells (sperm or egg), which would produce changes that are passed to the next generation. One potential route is to modify genes in the stem cells that produce sperm, which could lead to treatments for both male infertility (*below*) and single-gene disorders. (In 2015, for example, Chinese researchers used such an approach to fix a mutation that causes cataracts in mice.)


Spermatids
Mature sperm
Secondary spermatocytes
Primary spermatocyte
Spermatogonium
This process does not occur: Sperm fail to develop
Maturation is halted
Spermatogonial stem cell
Genome missing a functioning gene critical for sperm development
SSCs removed from patient
CRISPR tool (gold)
Cas9
Therapeutic gene
Therapeutic gene is introduced to the larger sequence, in this case, with an assist by a CRISPR tool, in which the Cas9 enzyme cuts the genome at a preselected spot.
SSCs screened, then reintroduced to patient testis
Mature egg
Primordial germ cell
Resulting offspring
Genome includes functional copy of the gene

Without Gene Modification

In healthy males, specialized adult cells in the testes known as spermatogonial stem cells (SSCs) produce millions of sperm each day. In many cases of male infertility, a dysfunctional gene in spermatogonial stem cells interrupts the complex process in which mature sperm cells form. Males with this condition, known as nonobstructive azoospermia, are usually incapable of producing sperm—and thus cannot have their own biological children.

With Gene Modification

A corrective approach, being pursued in animal research, would be to remove defective SSCs from infertile males and, using gene-editing techniques, replace the dysfunctional gene with an intact version through gene editing. One advantage of this approach is that the gene-edited stem cells can be screened both for correct insertion of the new gene and for any unwanted "off-target" hits. Cells that pass this safety check could be transplanted back into the patient to restore fertility. The genetic correction would then be passed on to the next generation—the very definition of germ-line modification.

cause science is already bumping up against the red line.

Despite a thicket of international provisions regulating human embryo research, Church and others believe that the creation of gene-edited sex cells in the test tube (the technical term is "in vitro gametogenesis," or IVG) has made great strides in recent years without attracting the same public scrutiny, or provoking the same ethical discomfort, as gene editing in embryos.

"In terms of the technology, that's ready to go now," says I. Glenn Cohen, a bioethicist at Harvard Law School. "In vitro gametogenesis is much closer to the mark than any other way to do it." And Ina Dobrinski, an expert in reproductive biology at the University of Calgary who works on gene editing of large animals such as pigs, adds, "Theoretically, we can do it. Practically [speaking], nobody is even touching it because of the ethical issues."

If human germ-line editing is inevitable, despite the ethical concerns (and indeed legal prohibitions in many countries), how might it happen? Speculation among biologists has become something of a parlor game, but I turned to Church, a card-carrying futurist, to lay out a plausible scenario. He was happy to oblige.

Church sees the germ-line Rubicon being crossed because sperm do not seem to arouse the same ethical passions as embryos or even egg cells. (Bioethicist Cohen agrees: "People do

Illustration by Jen Christiansen

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not believe that masturbation is genocide.") He also thinks gene therapy, not CRISPR per se, will set the table for this momentous change because it is already accepted: the U.S. Food and Drug Administration has allowed many trials of gene therapy in somatic (nongerm-line) cells. "Gene therapy is happening in young children already and will happen in younger and younger children," Church says.

In a highly publicized case in fall 2015, for example, British researchers used gene-editing techniques to alter the immune cells of an infant battling leukemia. And the leap to germ-line gene therapy, according to Church, will occur not in human embryos but in the most proletarian, plentiful and expendable cell in the human body: sperm. Gene-editing sperm will spare couples the agony of destroying IVF embryos that, on preimplantation screening, are shown to possess variants that forecast some devastating single-gene disorders, he believes. "Maybe half the people in the U.S. already feel that they're not comfortable killing embryos, but I think people would be comfortable genetically altering sperm," he observes.

Two obvious targets, Church adds, would be single-gene disorders (such as Tay-Sachs disease) and infertility. "You could also do it in human spermatogonial stem cells," he says, referring to the specialized adult stem cells in male testes that generate sperm cells—millions on millions of mindless, headlong swimmers—every day. "People don't really care about spermatogonia. Most people don't even know how to pronounce it. So they're going to let you mess around with them, right?" Church continues. "You will be able to do all kinds of things to show that they are functionally normal—that you've taken the sperm that can't swim, and that you've now taken their stem cells and made sperm that can swim. You can test that in a lab without any eggs being involved. And then in the fertility clinic, the dad will say, 'Hey, those are pretty awesome sperm. Let's try them out and see what they can really do.' And I don't know who's going to stop them from doing that."

As for the timeline, Church says, "I think there will be multiple clinical infertility solutions involving gene therapy soon."

How soon?

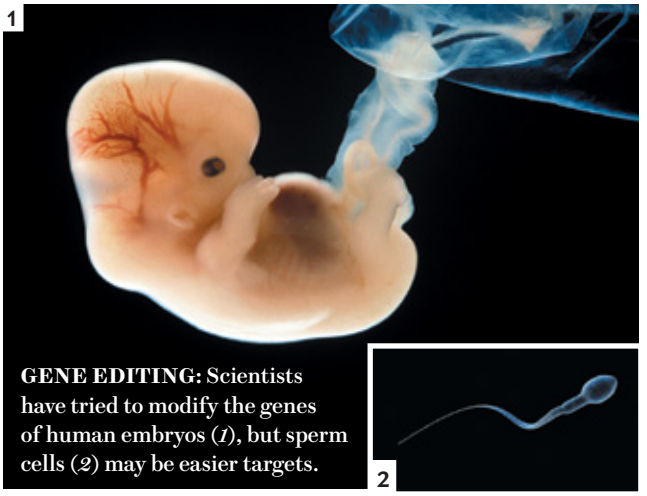
"The next couple years," he says. "It would be very hard to resist."

In his talk at the National Academies meeting, Orwig flashed a slide that said: "Germ-Line Gene Therapy Is Technically Feasible Today." Afterward, according to Orwig, a member of the planning committee sidled up to him backstage and said, "Germ-line gene therapy is going to happen, I guarantee it." That sentiment never made it into the final meeting communiqué. But it galvanized Orwig. "Whereas it might have been something I wanted to do hiding under a rock, it's now like, 'You go, man!' Let me get to work and prove to you that I can do it."

In animals, of course.

A GENTLE NUDGE DOWN THE SLOPE

A FEW STEPS DOWN the hallway from Orwig's office is a complex of rooms that houses hundreds of mice. Many of the cages contain what are called nude mice—pink, wrinkled little rodents that resemble scrotums with eyes and feet. They are nude in the sense that they were bred to have compromised immune systems that accommodate cells transplanted from other species—for instance, human spermatogonial stem cells with mutations—to allow researchers to better understand the biology of male infertility.



GENE EDITING: Scientists have tried to modify the genes of human embryos (*1*), but sperm cells (*2*) may be easier targets.

If, as Church says, "everything is going to be done in animals first," the road to human germ-line modification runs through rooms like these. CRISPR makes the task more efficient ("It is so freaking easy!" Orwig says), but scientists have been able to alter the genes of sperm-making cells for more than two decades, beginning in 1994, when University of Pennsylvania biologist Ralph Brinster (Orwig's mentor) did the pioneering experiments in mice.

Male infertility has many causes, including obstructive "plumbing" issues, glitches in the incredibly complex process of sperm creation, and underachieving sperm. But in many cases, males simply can't make sperm at all; the condition, known as nonobstructive azoospermia, affects roughly 350,000 men in the U.S., according to Orwig. Several genes have been associated with the failure to produce sperm, including *tex11* and *sohlh1,* and those cases form the backdrop of the experiment Orwig is eager to do.

What Orwig wants to do is take infertile mice, which have a dysfunctional version of one of these genes, remove the sperm-forming stem cells from their testes and correct the defect in those cells by using the new gene-editing techniques. Once the altered stem cells are grown to sufficient numbers in the test tube and screened for precisely the correct alteration, they can be transplanted back into the testes of the animals. And at least in animal experiments of this kind, there is no need for any fancy molecular tests—if the gene editing is successful, Orwig will know within a couple of months because the infertile males will unambiguously demonstrate their ability to become fathers.

"We've been transplanting stem cells for 25 years in almost every species—mice, rats, hamsters, sheep, goats, pigs, dogs and monkeys," Orwig says. "That's a pretty broad swath of evolution, and in all this time, in all these animals, as far as we know, nothing bad has happened." That is why Orwig is optimistic he can demonstrate that editing the genes of stem cells in mice can reverse infertility.

This may seem like an innocuous animal experiment, but to edit a sperm-forming stem cell is to permanently modify the germ line because the resulting sperm cells pass the correction along to the next generation. A potential treatment for male infertility would cross the red line. And although Orwig has no plans to do the obvious human follow-up in his Pittsburgh lab, a successful preclinical demonstration in mice and primates would provide the impetus for an attempt in the private sector—which is where

NEIL HARDING *Getty Images (1);* GETTY IMAGES (2)

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Church believes the final steps will unfold. "Sperm-editing efforts will be privately funded," he says, "just like other therapies."

Developing such a clinical treatment would face technical hurdles, of course. For one thing, scientists would have to find a way to maintain human spermatogonial stem cells long enough to select the right ones for transplantation—still not a trivial task. But these male stem cells offer much less of a moving target than embryos, which are dynamic and change rapidly. The Chinese researchers who have attempted gene editing in embryos with CRISPR, for example, have reported both "untoward mutations" and "mosaicism," meaning that some cells in the embryos show successful editing, whereas others do not. Moreover, the DNA of gene-edited stem cells can be screened before an embryo is produced.

That is what makes Orwig's potential mouse experiment so politically inconvenient. Because of prohibitions enacted by Congress in the 1990s, the National Institutes of Health cannot fund any research that involves the destruction of human embryos. A human version of Orwig's proposed mouse experiment might sidestep that prohibition, but it would probably fall under a new obstacle that the House of Representatives introduced two weeks after the December summit on gene editing. In a two-sentence passage buried in the 2,009-page omnibus spending bill of 2015, Congress inserted language forbidding the FDA to consider any medical intervention relying on the use of gene-edited embryos; the wording does not explicitly prohibit editing germ cells, but Stanford University law professor Henry Greely believes "the FDA would take the position that those sperm were more than minimally manipulated human cells that would require FDA approval as a drug or biological product." The regulatory piece, he thinks, could add a decade or two to Church's timeline.

That does not mean Orwig's mouse experiment would be against the law—just a gentle nudge down the slippery slope toward germ-line modification. The step across the red line could happen in private IVF clinics, which have a long (and blemished) history of pushing the envelope on new reproductive technologies. "It's such an easy technology to apply that it would only take somebody with a little chutzpah to get together with someone in an IVF clinic and, you know, take a shot at it," says George Daley, a stem cell biologist at Boston Children's Hospital. "This is coming down the pike, and people need to start thinking about it," he notes.

It probably will not happen in the U.S. unless the public—and political—perception of germ-line modification becomes more accommodating, but Orwig is quietly preparing for that day. "We're going to work real hard behind the scenes," he says, "until the worldview changes."

CROSSING BORDERS

THE "WORLDVIEW" on germ-line editing is complicated and contradictory. A majority of Americans do not like the idea of editing genes in either embryos or germ cells, according to a recent analysis of 17 public opinion polls published in the *New England Journal of Medicine*. Yet paradoxically, most people support gene editing in adults "aimed at preventing one's children from inheriting certain diseases." (Robert J. Blendon, lead author of the study, says any intervention on the adult side that is positive for the next generation, including germ cells, would have "considerable public support.") Moreover, the *NEJM* study also pointed out that many of these public opinion polls pose their questions using language that "might not be scientifically precise." In other words, although the National Academies meeting adjourned in December 2015 with a pledge to continue the public conversation about germ-line editing, it is not clear that the public even understands the terms of that conversation. While public forums struggle to find an effective vocabulary, the science races ahead.

As we spoke in his office in spring 2016, Orwig nodded at a scientific reprint sitting on his desk. "I really, really love this paper," he said. He was referring to research published in the March 3, 2016, issue of *Cell Stem Cell* by a group headed by Qi Zhou of the Chinese Academy of Sciences. The experiment basically provided a recipe for the in vitro creation of germ cells.

The researchers showed that they could create sperm-forming stem cells in a dish; with a technique currently used in IVF clinics, these cells could be injected into egg cells to create fertile male mice. Harvard's Daley says of this advance: "With the addition of CRISPR, you've got the brave new world."

When Aldous Huxley imagined his brave new world in 1932, the story unfolded under one totalitarian regime, with neither national boundaries nor local regulations. In today's world, germ-line editing in any one place means the germ line is edited everywhere. "Regulation is country-specific, but science crosses borders," Harvard Law's Cohen says. Even if there were laws against germline modification in the U.S., you would have to build a wall much higher than the one proposed by Donald Trump to keep American germ lines insulated from an eventual influx of modified DNA.

"If you play out the world to 100 years from now, if anybody does this anywhere, that's the end game," Cohen says. "Over time those people will mate and create offspring and will cross borders and enter our shores. And if the safety and efficacy are worked out, it's inevitable that you're going to have people walking around in the world, and they're going to be reproducing, and they will end up in this country, and those changes will enter the U.S. gene pool."

As I am concluding my visit with Orwig, he glances at the computer on his desk. A reporter has sent an e-mail seeking comment on yet another experiment cozying up to the red line: a group in China has just reported its attempt to edit human embryos (nonviable) to be resistant to HIV infection. "Eventually we'll learn a vocabulary that acknowledges that we're there," Orwig says. "But I feel we're already there." SA

Stephen S. Hall is an award-winning science writer. He has authored six books, including histories of recombinant DNA and cancer immunotherapy, and teaches science communication at New York University.

MORE TO EXPLORE

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FROM OUR ARCHIVES

Editing the Mushroom. Stephen S. Hall; March 2016.

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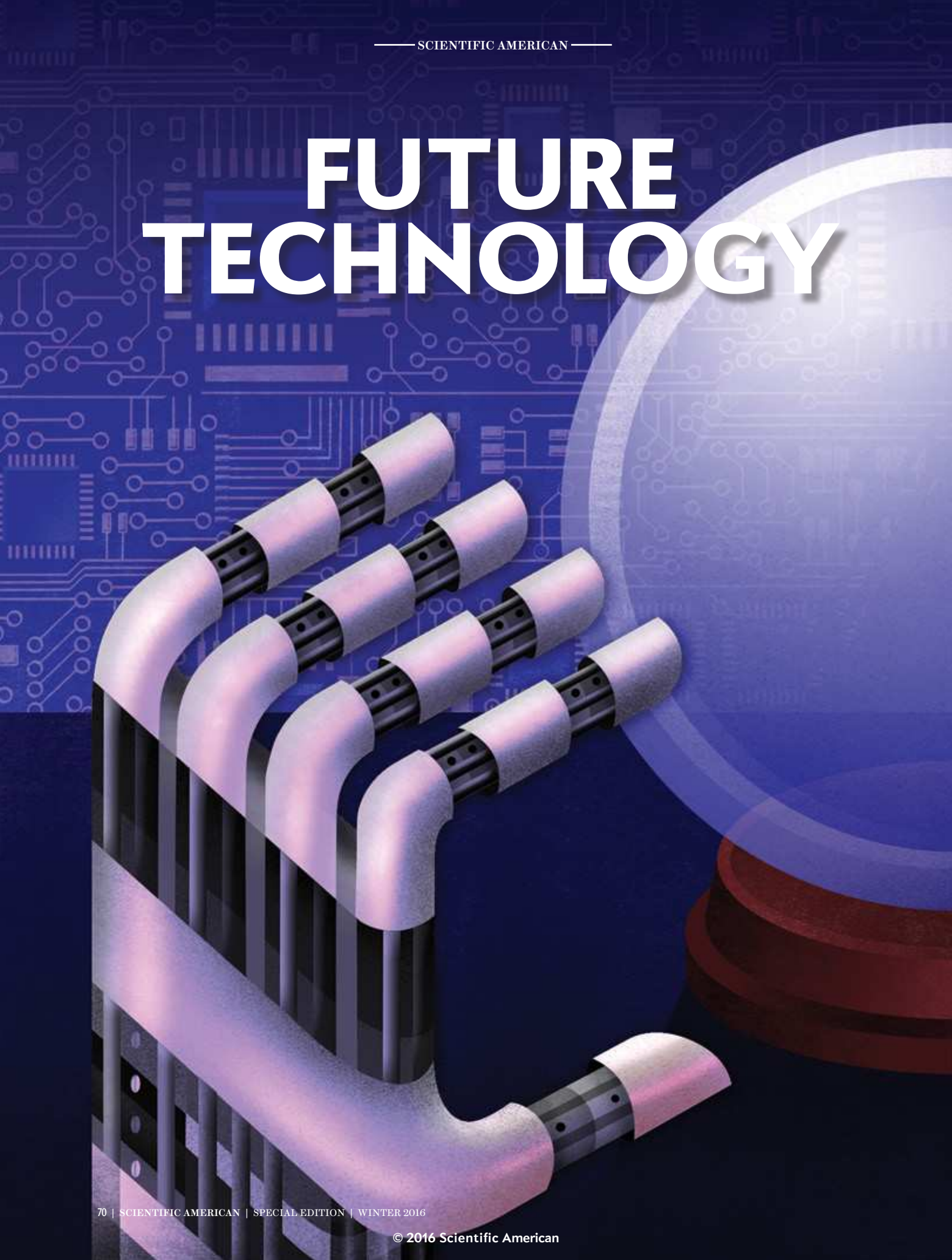
FUTURE TECHNOLOGY



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Computers are already ubiquitous. Soon they might start changing form entirely and making broader inroads into our daily lives. Scientists working in the field of biological computing are close to programming living cells so that they can diagnose human disease and repair environmental damage (*page 72*). Automakers are racing to automate cars, although they face a number of challenges before self-driving vehicles can become ubiquitous (*page 78*). And people have begun to ask seriously: Could we be living in a computer simulation right now (*page 84*)?

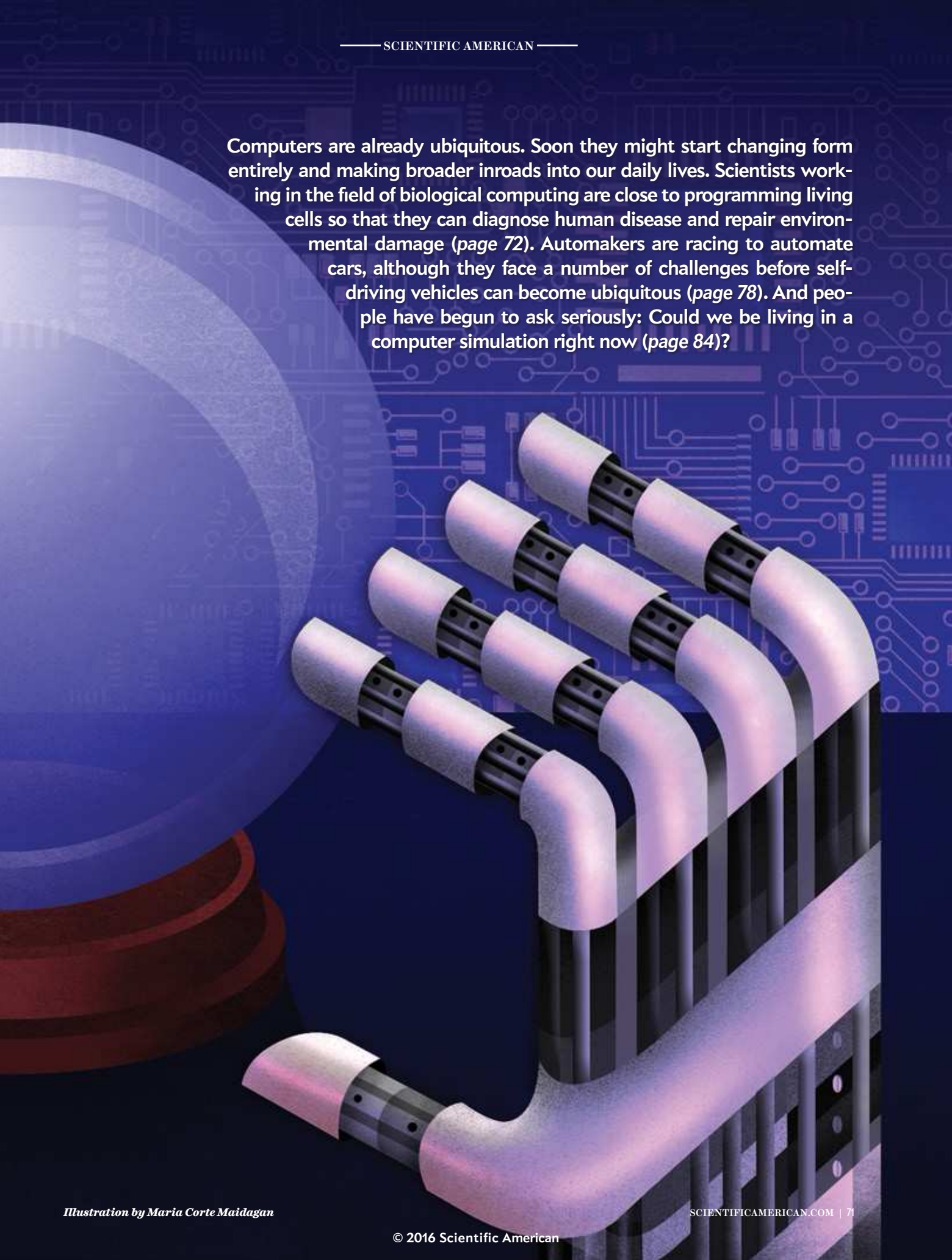

Illustration by Maria Corte Maidagan

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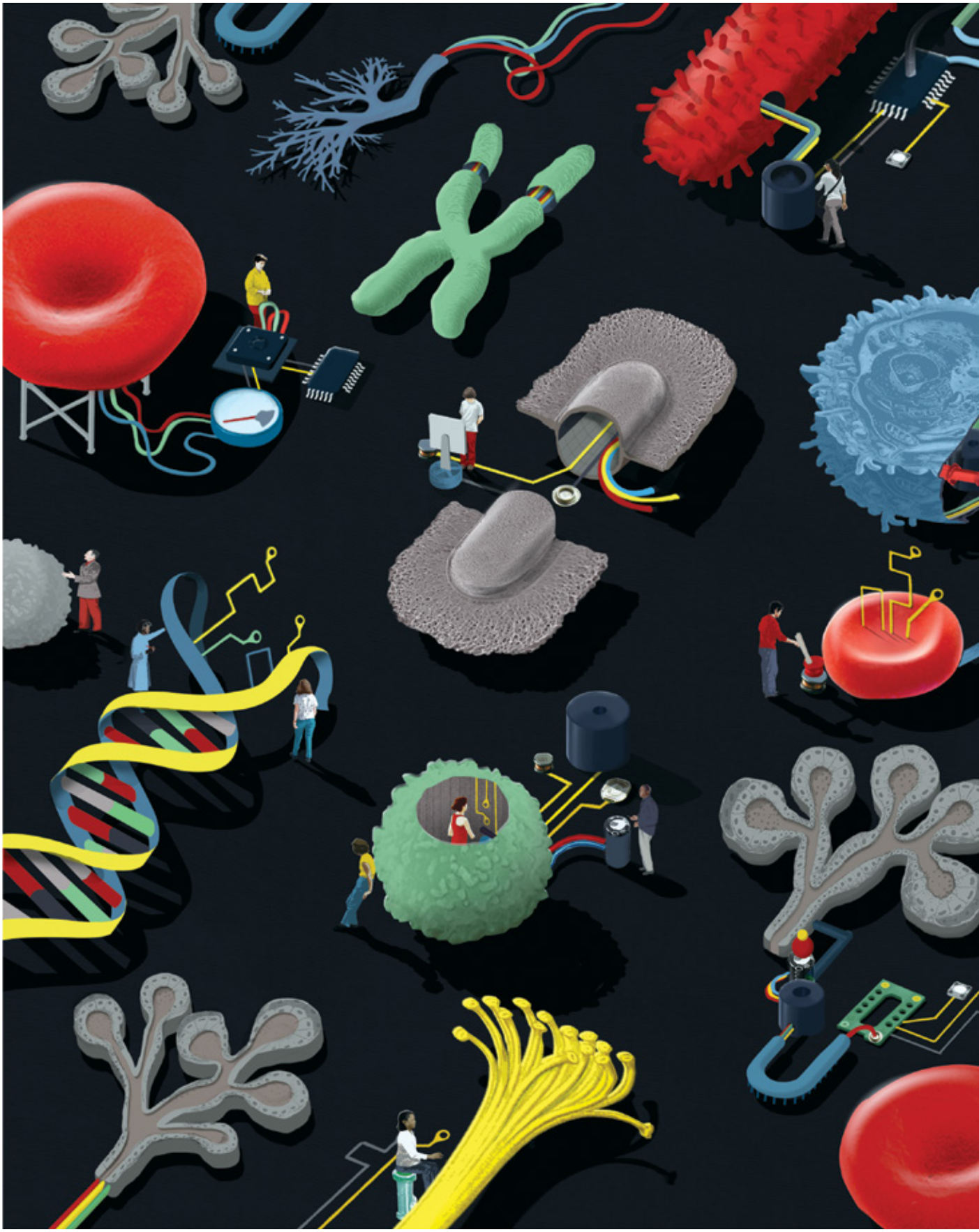

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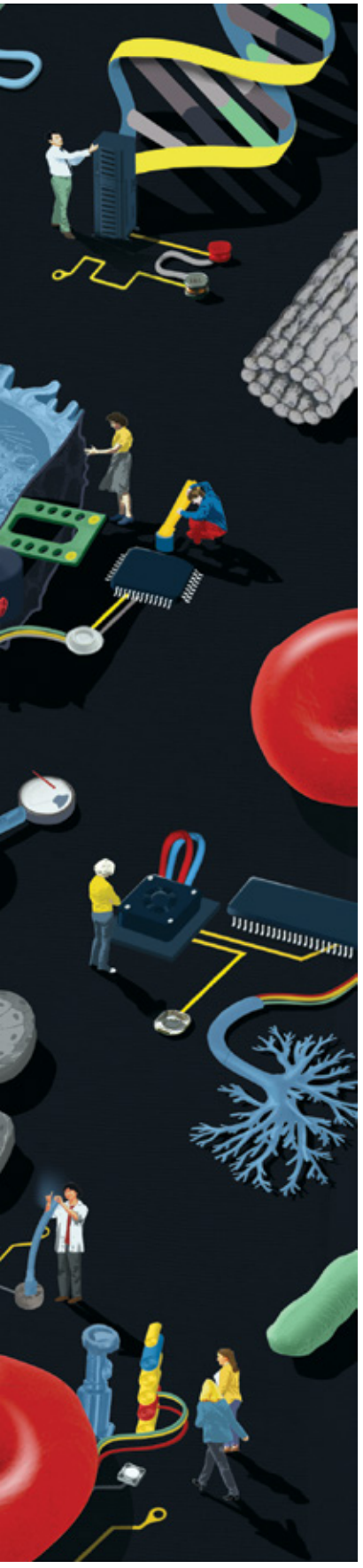

BIOENGINEERING

MACHINE LIFE

Synthetic biologists are close to putting living cells to work diagnosing human diseases and repairing environmental damage

By Timothy K. Lu and Oliver Purcell

THE FIRST COMPUTERS WERE BIOLOGICAL: they had two arms, two legs and 10 fingers. "Computer" was a job title, not the name of a machine. The occupation vanished after programmable, electric calculating machines emerged in the late 1940s. We have thought of computers as electronic devices ever since.

Over the past 15 years or so, however, biology has been making a comeback of sorts in computing. Scientists in universities and biotech start-ups believe they are close to advancing the first biocomputers from mere research objects to useful, real-world tools. These systems, built out of genes, proteins and cells, include basic elements of computer logic: IF/THEN tests, AND and OR operations, even simple arithmetic operations. Some systems include primitive digital memories. Given appropriate biological inputs, these living computers generate (mostly) predictable outputs.

Within about the next five years, the first biological computers might be used as sensitive and accurate diagnostics and therapeutics for human diseases, among them cancer, inflammatory diseases and rare metabolic disorders. We and others who are engineering these cellular logic systems envision a future—one not far off—in which they are safe and smart enough to treat disorders as well as identify them. The technology could make it possible to produce complex chemicals, such as biofuels and pharmaceuticals, in novel ways that are faster and less expensive than we can create today. It might allow us to re-

Illustration by Sam Falconer

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spond to spills by lacing contaminated ecosystems with organisms designed to monitor and degrade toxins.

That is not to say that biocomputing technology is now advanced. On the contrary, the field is in its infancy. Don't think iPhone—think Colossus.

Colossus was one of the first programmable electronic computers. Had you walked into Bletchley Park, the top-secret code-breaking center north of London where Colossus began operating in 1944, you would have seen it whirring away, paper tape streaming over pulleys, 1,600 vacuum tubes humming. By today's standards, Colossus was laughably primitive. It filled a room—hence the name. It could do only a few kinds of calculations and could not store its own program. It took days or weeks to design, load and test a new program. Operators had to physically rewire the machine each time.

Despite its limitations, Colossus was able to break the encryption the Nazis used to encode their most important messages. That clunky toddler of a computer helped to win a World War. And its descendants propelled civilization, decades later, from the industrial age to the information age.

The most impressive cellular computers made so far are actually much simpler, slower and less capable than Colossus. Like the earliest electronic, digital computers, they do not always work, they run only the simplest programs and they are not reprogrammable outside the laboratory. But we see in this technology some of the same transformative potential for society that digital electronics had in its formative years. Even a tiny bit of smarts, applied cleverly, can create near-magical results in a living system.

Cellular computers are not likely to ever replace the electronic and optical variety. Biology will not win any races against solid-state physics. But the chemistry of life has a unique power of its own, and it can interface with the natural world—much of which, after all, runs on biology—in ways that electronic systems cannot.

SWITCH ON, SWITCH OFF

EVERY CELL in your body is, in some sense, a little computer. The cell receives inputs, often in the form of biochemical molecules attaching to its surface. It processes these inputs through intricate cascades of molecular interactions. Sometimes those reactions affect the activity level of one or more genes in the cell's DNA—that is, how much a given gene is "expressed" by being transcribed into RNA and then translated into multiple copies of the protein molecule the gene encodes. This analog, chemical computation generates outputs: a squirt of hormone from a gland cell, an electrical impulse from a nerve cell, a stream of antibodies from an immune cell, and so on.

As synthetic biologists, we aim to exploit those natural information-processing abilities of cells to run programs that we design. We aspire to go well beyond conventional genetic engineering that just "knocks out" a gene, or cranks up its expression, or inserts a gene or two from one species into cells of a different species. Our goal is to be able to quickly and reliably tailor the behavior of many different varieties of cells (or populations of cells) in much the same way that an electrical engineer designs a circuit board: by choosing standardized parts from a catalog and wiring them together. Unfortunately, biology is different from electronics in ways that frustrate that ambition—more on that later.

The field has made slow but considerable progress. The first big advances came in 2000. That year James Collins and his colleagues, then at Boston University, stitched together two mutually interfering genes to make a genetic switch that can be toggled between two stable states—a one-bit digital memory. In addition, a group led by Michael Elowitz, then at Princeton University, engineered a rudimentary oscillator into a strain of the bacterium *Escherichia coli*. The transformed microbe blinked like a Christmas light as a fluorescence gene turned on and off periodically.

By 2003 Ron Weiss, then at Princeton, had designed a "Goldilocks" biocircuit that causes a cell to light up when the concentration of an environmental compound is just right: not too high, not too low. That system linked together four inverters, which change a HIGH signal to a LOW signal, and vice versa.

A few years later Adam Arkin and his colleagues at the University of California, Berkeley, came up with a heritable form of memory that, when triggered, uses enzymes called recombinases to snip small sections out of the DNA, flip them backward and then put them back into place. The modified DNA segment passes from a cell to its daughters when that cell divides—a useful feature, considering that many bacteria reproduce every hour or two.

Crafting single-operation parts is one thing; cobbling many parts into an integrated system is much trickier but much more useful. Synthetic biologists have created genetic parts to perform all the basic Boolean operations of digital logic (AND, OR, NOT, XOR, and so on). By 2011 two groups of researchers had inserted individual logic gates into bacterial cells and programmed the cells to communicate with one another through chemical "wires," essentially creating multicellular computers.

Martin Fussenegger, Simon Ausländer and their colleagues at the Swiss Federal Institute of Technology Zurich then assembled such parts to create still more advanced systems that could perform simple arithmetic. One of us (Lu), working with Collins, George Church of Harvard Medical School, and others, combined heritable memory units into a cascade to yield an engineered strain of *E. coli* that can count to three. The memory state remains intact in this system from one generation of cell to the next. That is a crucial feature because it allows information about past biochemical events to be stored for retrieval at some reasonably distant time in the future. In principle, the counter we made could be enhanced to reach higher numbers and to record important biological events, such as cell division or cellular suicide.

IN BRIEF

Bioengineers have created living cells that can count, add, store data in memory and perform basic logic operations.

These biocomputers communicate using chemical signals, which are inherently noisy. Designers also have trouble predicting how biocomputers will perform before they are built: we simply do not know enough about how cells work.

Research laboratories and companies are testing applications, including ingestible cells that treat metabolic disorders.

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A FEATURE *AND* A BUG

BIOLOGICAL COMPUTING has begun moving beyond proof-of-concept demonstrations; potential real-world applications are now in sight. Within the past several years we and others have found many ways to engineer sensors, logic operators and memory components into genetic circuits that can carry out truly useful tasks in living cells.

In 2011, for example, a group that included Weiss, now at the Massachusetts Institute of Technology, Zhen Xie, now at Tsinghua University in China, and Yaakov Benenson of the Swiss Federal Institute of Technology Zurich created a far more advanced genetic logic system that can force a cell to self-destruct if it contains a specific cancerous signature. The genetic circuit monitors the levels of six different biological signals—in this case, short pieces of RNA called microRNAs that regulate gene expression. The six microRNA signals form a distinct signature of human-derived cancer cells known as HeLa cells. When the circuit is in a HeLa cell, it triggers a genetic kill switch and produces a protein that directs the cell to commit suicide. In a non-HeLa cell, the circuit is inactive and does not trigger cell suicide.

Other research groups, including our own, have demonstrated biocomputing circuits that can perform basic arithmetic (addition or subtraction), compute ratios or logarithms, convert two-bit digital signals to analog output levels of a protein, and record and transmit the on/off states of all their logic gates from the parent cell to its children.

In 2015 our group, along with Christopher Voigt's group, both at M.I.T., developed a biocomputing microbe that works inside a mammal's gut. We used mice as test subjects, but the bacterial species we modified, *Bacteroides thetaiotaomicron,* is found naturally and at very high levels in the gut of roughly half of adult humans. Previously, Pamela Silver of Harvard Medical School and her colleagues engineered *E. coli* to operate in the mouse gut.

The biocircuit turns the bacterium into a spy. While the microbe loiters inside the gut, it uses part of its DNA like a notebook to detect whether it has bumped into a predetermined chemical. We targeted innocuous compounds that we could feed to the mice, but the target could easily be a toxic molecule or biomarker present only when the host has a particular disease.

After ingesting the compounds, the mice excrete the surveillance bacteria in their droppings. In those microbes that recorded an exposure to the target, the circuits trigger production of luciferase, an enzyme that glows in the dark. The telltale glow is faint, but we can see it under a microscope.

It is not hard to imagine how such biocomputing systems could be helpful to people who have a gut condition, such as inflammatory bowel disease (IBD) [*see box on next page*]. Soon we may be able to program innocuous, naturally occurring bacteria to seek out and report on early signs of cancer or IBD. The devices could change the color of the stool—or add a chemical to it that is detectable by using an inexpensive kit similar to a home pregnancy test.

THE HARD PARTS OF WETWARE

CELLULAR SENTRIES like those we just described do not need much computational power to greatly improve on the diagnostic tests already available. An IF/THEN test, a few AND and OR gates, and one or two bits of persistent memory are sufficient. That is fortunate because biocomputer engineers face a long list of hard challenges that electronic computer engineers never had to deal with.

Compared with the gigahertz speeds of electronic circuits, for example, biology proceeds at a snail's pace. When we apply inputs to our genetic systems, it typically takes hours for the output to emerge. Fortunately, many biological events of interest do not operate on extremely short timescales. Nevertheless, researchers continue to look for faster ways to compute in living cells.

Communication poses a separate problem. In conventional computers, avoiding cacophony is easy: you simply connect components by wires. When many components have to share a wire, you can give each one its own little window of time to speak or listen by synchronizing each part to a universal clock signal.

But biology is wireless, and there is no master clock. Communication within and between cells is inherently noisy, like radio. One reason for the noise is that biological parts use chemicals rather than physical wires to signal one another. All the components that use any particular chemical "channel" can talk at the same time. What is worse, the underlying chemical reactions that send and receive signals are themselves noisy; biochemistry is a game of probabilities. Designing systems that compute reliably despite noisy signals is a continual challenge.

These issues especially plague biocomputing systems that use analog computing, as many do, because, like slide rules, they depend on values (the levels of proteins or RNAs) that can vary nearly continuously. Digital systems, in contrast, process signals that are either HIGH or LOW, TRUE or FALSE. Although that makes digital logic more robust to noise, many fewer parts are available that work this way.

The biggest problem we face is unpredictability, which is a polite way of saying ignorance. Electrical engineers have numerical models that predict, with near-perfect precision, what a new circuit design will do before they build it. Biologists simply do not understand enough about how cells work—even simple ones like bacteria—to make the same kind of predictions. We feel our way forward, largely by trial and error and often find that when our systems function, they do so only for a while. Then they fall apart. Many times we do not understand why.

But we are learning—and one important reason to build computers out of cells is that this process of building, testing and debugging biological computers can uncover subtleties of cellular biology and genetics that no one had noticed before.

BIRTH OF A NEW MACHINE

IT MAY TAKE DECADES to conquer all these challenges; some, such as the relatively slow speed of biological processing, may be forever intractable. Thus, it seems unlikely that biocomputing will grow in performance at the same exponential trajectory that digital electronic computing did. We do not expect that biological computers will ever be faster than conventional computers for mathematical computation or pushing data around. Biocomputer engineers do benefit, however, from an ever accelerating increase in the rate at which we can read and synthesize raw DNA. Like Moore's law, that trend reduces the time it takes us to design, build, test and refine our gene circuits every year.

Although it is still early days, commercially viable applications of biocomputing are coming. Cells can navigate living tissue, discriminate among complex chemical signals, and stimu-

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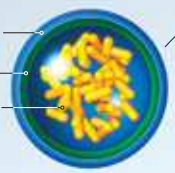
Diagnosis by Biocomputer

Biological computing systems could have myriad applications in agriculture, pharmaceutical manufacturing and medicine. Inserting even a tiny bit of computing logic into a living cell can yield tremendously useful behavior.

Research laboratories are already working, for example, to engineer bacteria that could be safely swallowed as a pill, travel through the digestive system and detect specific signs of disease in the gut. Doctors could then quickly make a reliable diagnosis by placing a swab of the patient's stool into an automated reader. Such technology could remove much of the uncertainty, delay and misdiagnosis that often occurs in gastroenterology.



1 A biocomputing diagnostic for inflammatory bowel disease (IBD) could take the form of a small pill containing millions of bacteria, perhaps from a strain of *Bacteroides thetaiotaomicron*, which normally lives in the human gut. Each bacterium contains multiple computing elements (*described at far right*).

2 An outer protective coating on the pill dissolves away in the small intestine, releasing the bacterial payload into the gut. As the bacteria move through the intestines, the sensors engineered into them are able to detect the simultaneous presence of two or more distinctive biological signals—signals that occur together only when the patient has IBD.

3 As the bacteria move through the colon and into the rectum, the disease signals may disappear from the gut, but memory elements encoded in the bacteria's DNA preserve the information.

4 The bacteria exit the body along with the rest of the stool. Each engineered cell that detected the diagnostic signal at some point along its journey produces many copies of a luminescent protein that glows faintly and can be detected by an automated reader. The system can provide the information that a patient and doctor need to decide on a treatment.

Illustration by Bryan Christie

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late growth and healing in ways that no microchip ever could. If biocomputer diagnostics work well, the next logical step is to use them to treat disease when and where they detect it.

Cancer treatment clinics have already started isolating immune system cells known as T cells from patients who have blood cancer, inserting genes into the T cells that direct them to kill the cancer and then injecting them back into the body. Researchers are now working to add logic to the genetic package that gets loaded into the T cells so that they can recognize multiple cancer signatures and be equipped with off switches that doctors can use to control them. Many other kinds of cancer might become treatable by this approach.

In 2013 Collins and Lu got together with several other biologists to found Synlogic, a company to commercialize medicines that use modified probiotic bacteria that can be safely swallowed. The start-up is now refining biocomputers intended to treat phenylketonuria and urea cycle disorders, two rare but serious metabolic disorders that affect people from birth. Animal trials have begun, with encouraging results.

As we gain deeper insight into how the microbiome affects human health, we should find engineered bacteria to be beneficial therapeutics for a widening array of diseases—not just cancer but also inflammatory, metabolic and cardiovascular disorders. With growing experience and an ever increasing library of bioparts, "smart" medicines will become more common and more powerful. Moreover, the technology seems likely to spread from medicine to other areas. In the energy sector, smart bugs may be efficient producers of biofuels. In chemical and materials engineering, biocomputers may prove useful in synthesizing products that are currently hard to make or in exerting just-in-time control over biomanufacturing. In environmental conservation, biocomputers could monitor remote locations for cumulative exposure to toxic substances and then perform remediation.

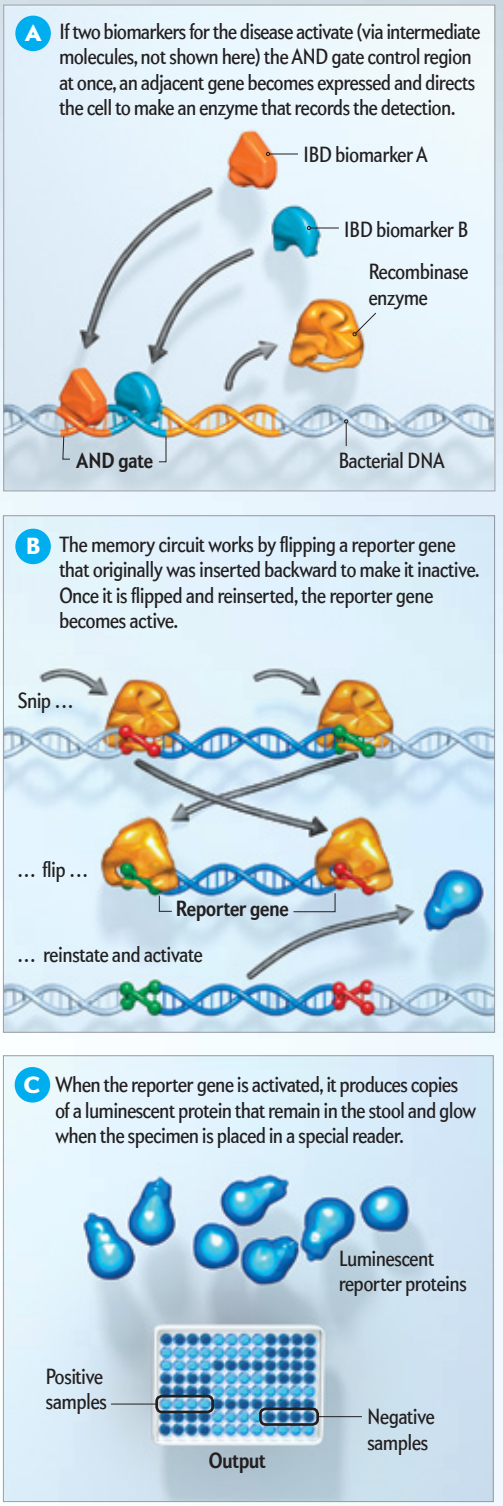
The field is rapidly evolving—literally. Almost certainly, the most amazing uses of biocomputing have yet to be conceived. SA

Timothy K. Lu is an associate professor leading the Synthetic Biology Group at the Massachusetts Institute of Technology, which integrates memory and computational circuits in living cells, applies synthetic biology to important medical and industrial problems, and builds living biomaterials. He is a recipient of a National Institutes of Health Director's New Innovator Award, among others. In 2014 he co-founded the synthetic biology start-up Synlogic.

Oliver Purcell is a postdoctoral associate in the Synthetic Biology Group at M.I.T. His research spans many areas of synthetic biology, from the design of synthetic biological parts to novel computational approaches for the rational design of biological systems.

How It Works

Bioengineers could transform living bacteria into a diagnostic for inflammatory bowel disease by making just a few small additions to the bacteria's genome. These additions include two sensors that function together as a Boolean AND gate, along with a memory circuit and a gene that yields a luminescent output signal.


A
If two biomarkers for the disease activate (via intermediate molecules, not shown here) the AND gate control region at once, an adjacent gene becomes expressed and directs the cell to make an enzyme that records the detection.
IBD biomarker A
IBD biomarker B
Recombinase enzyme
AND gate
Bacterial DNA
B
The memory circuit works by flipping a reporter gene that originally was inserted backward to make it inactive. Once it is flipped and reinserted, the reporter gene becomes active.
Snip …
… flip …
Reporter gene
… reinstate and activate
C
When the reporter gene is activated, it produces copies of a luminescent protein that remain in the stool and glow when the specimen is placed in a special reader.
Luminescent reporter proteins
Positive samples
Negative samples
Output

MORE TO EXPLORE

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FROM OUR ARCHIVES

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TRANSPORTATION

THE TRUTH ABOUT "SELF-DRIVING" CARS

They are coming, but not the way you may have been led to think

By Steven E. Shladover

Illustration by Tavis Coburn

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SOON ELECTRONIC CHAUFFEURS WILL TAKE US WHEREVER WE WANT to go, whenever we want, in complete safety—as long as we do not need to make any left turns across traffic. Changing road surfaces are a problem, too. So are snow and ice. It will be crucial to avoid traffic cops, crossing guards and emergency vehicles. And in an urban environment where pedestrians are likely to run out in front of the car, we should probably just walk or take the subway.

All these simple, everyday encounters for human drivers pose enormous problems for computers that will take time, money and effort to solve. Yet much of the public is becoming convinced that fully automated vehicles are just around the corner.

What created this disconnect? Part of the problem is terminology. The popular media applies the descriptors "autonomous," "driverless" and "self-driving" indiscriminately to technologies that are very different from one another, blurring important distinctions. And the automotive industry has not helped clarify matters. Marketers working for vehicle manufacturers, equipment suppliers and technology companies carefully compose publicity materials to support a wide range of interpretations about the amount of driving their products automate. Journalists who cover the field have an incentive to adopt the most optimistic forecasts—they are simply more exciting. The result of this feedback loop is a spiral of increasingly unrealistic expectations.

This confusion is unfortunate because automated driving is coming, and it could save lives, reduce pollution and conserve fuel. But it will not happen in quite the way you have been told.

DEFINING AUTOMATED DRIVING

DRIVING IS A MUCH MORE COMPLEX ACTIVITY than most people appreciate. It involves a broad range of skills and actions, some of which are easier to automate than others. Maintaining speed on an open road is simple, which is why conventional cruise-control systems have been doing it automatically for decades. As technology has advanced, engineers have been able to automate additional driving subtasks. Widely available adaptive cruise-control systems now maintain proper speed and spacing behind other vehicles. Lane-keeping systems, such as those in new models from Mercedes-Benz and Infiniti, use cameras, sensors and steering control to keep a vehicle centered in its lane. Cars are pretty smart these days. Yet it is an enormous leap from such systems to fully automated driving.

A five-level taxonomy defined by SAE International (formerly the Society of Automotive Engineers) is useful for clarifying our thinking about automated driving. The first three rungs on this ladder of increasing automation (excluding level zero, for no automation) are occupied by technologies that rely on humans for emergency backup. Adaptive cruise control, lane-keeping systems, and the like belong to level one. Level-two systems combine the functions of level-one technologies—the lateral and longitudinal controls of lane-keeping and adaptive cruise-control systems, for example—to automate more complex driving tasks. This is as far as commercially available vehicle automation goes today. Level-three systems would allow drivers to turn on autopilot in specific scenarios, such as freeway traffic jams.

The next two levels are profoundly different in that they operate entirely without human assistance. Level-four (high-automation) systems would handle all driving subtasks, but they would operate only in strictly defined scenarios—in enclosed

IN BRIEF

The auto industry and the press have oversold the automated car. Simple road encounters pose huge challenges for computers, and robotic chauffeurs remain decades away.

Automated driving systems that rely on humans for backup are particularly problematic. Yet in the next decade we will see automatic-driving systems that are limited to specific conditions and applications.

Automatic parking valets, low-speed campus shuttles, closely spaced platoons of heavy trucks and automatic freeway-control systems for use in dedicated lanes are all feasible and perhaps inevitable.

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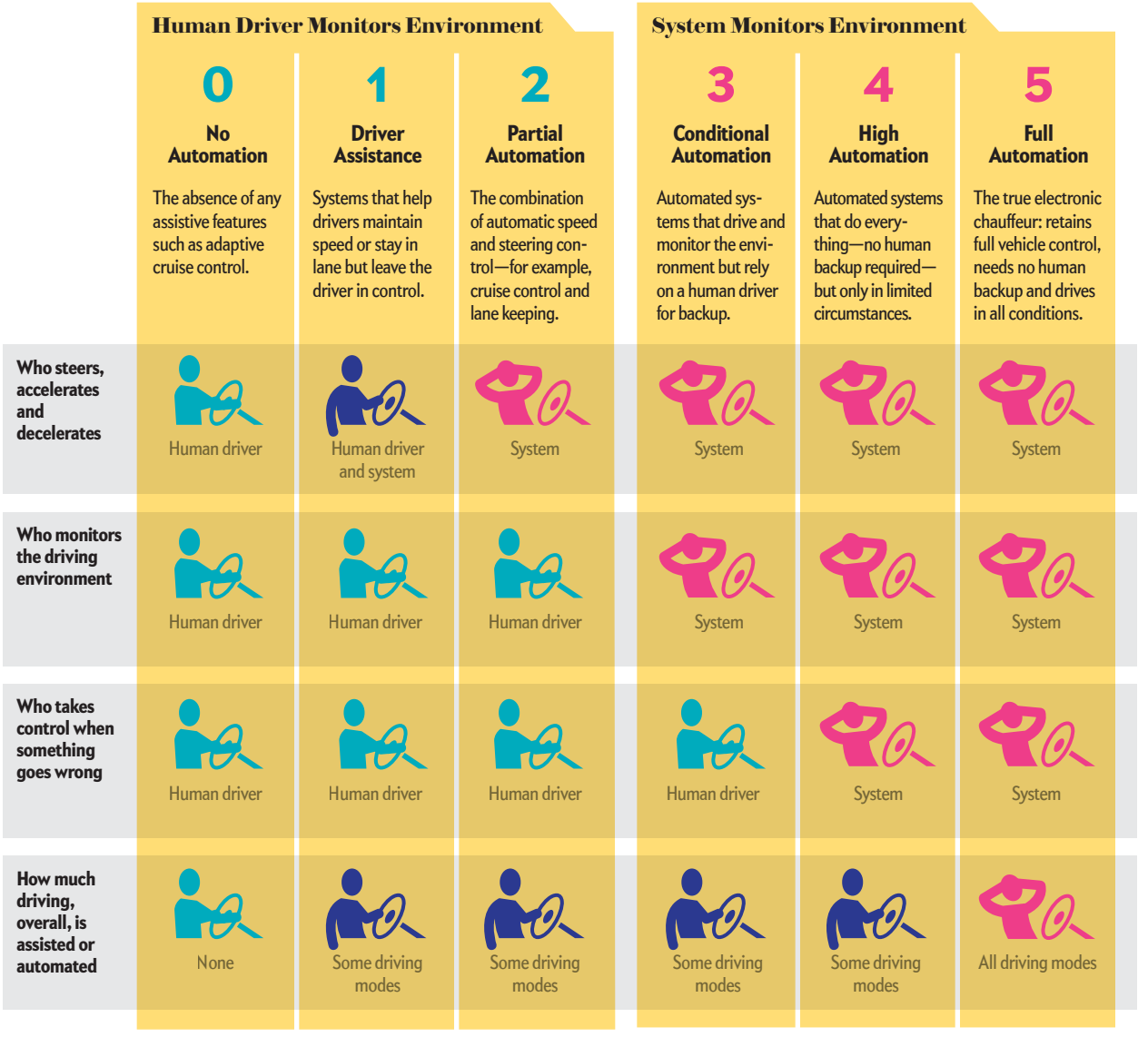
TAXONOMY

The Ladder of Automation

The automotive industry and the media have made a mess of the terminology used to talk about automated driverless systems. The terms "autonomous," "driverless" and "self-driving" obscure more than they illuminate. To clear things up, SAE International wrote definitions, paraphrased here, for different levels of automation and arranged them on a ladder of decreasing reliance on the driver. The hierarchy reveals some surprises. For example, level-four automation is potentially more tractable than level three. Level-five automated systems—electronic chauffeurs that can handle any driving condition with no human input—are decades away.



SOURCE: SAE INTERNATIONAL (WWW.SAE.ORG/MISC/PDFS/AUTOMATED_DRIVING.PDF); FOR DOCUMENTATION, INCLUDING ORIGINAL DEFINITIONS IN THEIR ENTIRETY, SEE *TAXONOMY AND DEFINITIONS FOR TERMS RELATED TO ON-ROAD MOTOR VEHICLE AUTOMATED DRIVING SYSTEMS*. SAE INTERNATIONAL, JANUARY 2014

parking garages, for example, or in dedicated lanes on the freeway. At the top of the ladder is level five—the fully automated car. Presumably, this is what many people have in mind when they hear someone such as Nissan CEO Carlos Ghosn confidently proclaim that automated cars will be on the road by 2020.

The truth is that no one expects level-five automation systems to be on the market by then. In all likelihood, they are a long way off. Level-three systems might be just as remote. But level four? Look for it within the next decade. To understand this confusing state of affairs, we have to talk about software.

SOFTWARE NIGHTMARE

DESPITE THE POPULAR PERCEPTION, human drivers are remarkably capable of avoiding serious crashes. Based on the to-

Illustrations by Nigel Holmes (icons)

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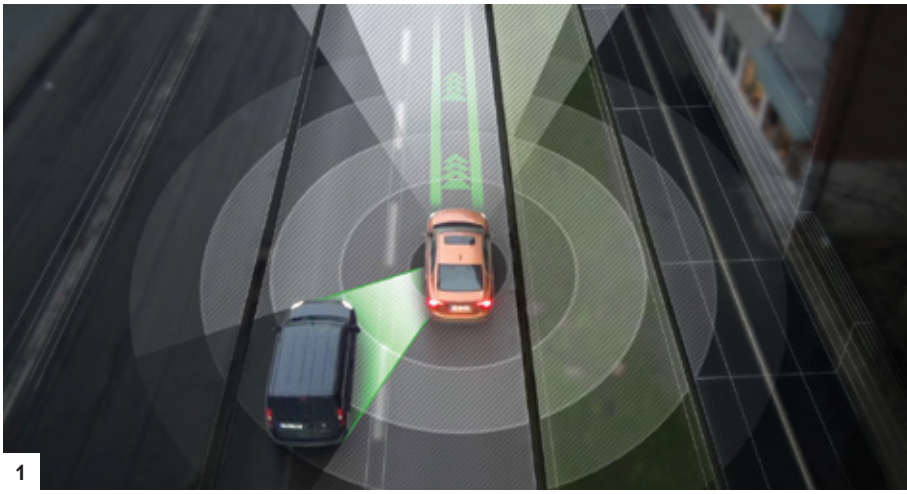
tal U.S. traffic safety statistics for 2011, fatal crashes occurred about once for every 3.3 million hours of driving; crashes that resulted in injury happened approximately once for every 64,000 hours of driving. These numbers set an important safety target for automated driving systems, which should, at minimum, be no less safe than human drivers. Reaching this level of reliability will require vastly more development than automation enthusiasts want to admit.



1

Think about how often your laptop freezes up. If that software were responsible for driving a car, the "blue screen of death" would become more than a figure of speech. A delayed software response of as little as one tenth of a second is likely to be hazardous in traffic. Software for automated driving must therefore be designed and developed to dramatically different standards from anything currently found in consumer devices.

Achieving these standards will be profoundly difficult and require basic breakthroughs in software engineering and signal processing. Engineers need new methods for designing software that can be proved correct and safe even in complex and rapidly changing conditions. Formal methods for analyzing every possible failure mode for a piece of code before it is written exist—think of them as mathematical proofs for computer programs—but only for very simple applications. Scientists are only beginning to think about how to scale up these kinds of tests to validate the incredibly complex code required to control a fully automated vehicle.

Once that code has been written, software engineers will need new methods for debugging and verifying it. Existing methods are too cumbersome and costly for the job. To put this in perspective, consider that half of the cost of a new commercial or military aircraft goes toward software verification and validation. The software on aircraft is actually much *less* complex than what will be needed for automated road vehicles. An engineer can design an aircraft autopilot system knowing that it will rarely, if ever, have to deal with more than one or two other aircraft in its vicinity. It does not need to know the velocity and location of those aircraft with incredible precision, because they are far enough apart that they have time to act. Decisions must be made on the order of tens of seconds. An automated road vehicle will have to track dozens of other vehicles and obstacles and make decisions within fractions of a second. The code required will be orders of magnitude more complex than what it takes to fly an airplane.

Once the code is validated, manufacturers will need ways to "prove" the safety of a complete automated driving system to the satisfaction of company risk-management officers, insurance firms, safety advocates, regulators and, of course, potential customers. The kind of formal "acceptance tests" used today are completely impractical for this purpose. Testers would have to put hundreds of millions, if not billions, of miles on a vehicle to ensure that they have subjected it in a statistically significant way to the dangerous scenarios it will encounter when it is regularly used by thousands of customers. People have started to think about solutions to this problem—the German government and industry have launched a multimillion-dollar project with that goal—but those efforts have just begun.

The code that will control the vehicle—the brain, so to speak—is not the only thing that must be subjected to scrutiny. The sensors that provide that brain with the data it will use to make decisions must be subjected to equal scrutiny. Engineers must develop new sensor-signal processing and data-fusion algorithms that can discriminate between benign and hazardous objects in a vehicle's path with nearly zero false negatives (hazardous objects that were not identified) and extremely low false positives (benign objects that were misclassified, leading to inappropriate responses from vehicles, such as swerving or hard braking).

Engineers cannot resort to the kind of brute-force redundancy used in commercial aircraft systems to achieve these goals because an automated car is a consumer product: it must be affordable for the general public. Turning to artificial intelligence is not an obvious solution, either. Some people have suggested that machine-learning systems could enable automated driving systems to study millions of hours of driving data and then learn throughout the course of their life cycle. But machine learning introduces its own problems because it is nondeterministic. Two identical vehicles can roll off the assembly line, but after a year of encountering different traffic situations, their automation systems will behave very differently.

LEVEL-FOUR FUTURE

I USED TO TELL PEOPLE that level-five fully automated driving systems would not become feasible until after 2040. Somewhere along the way people started quoting me as saying level five would arrive *in* 2040. Now I say that fully automated vehicles capable of driving in every situation will not be here until 2075. Could it happen sooner than that? Certainly. But not by much.

The prospects for level-three automation are clouded, too, because of the very real problem of recapturing the attention, in an emergency, of a driver who has zoned out while watching the scenery go by or, worse, who has fallen asleep. I have heard representatives from some automakers say that this is such a hard problem that they simply will not attempt level three. Outside of traffic-jam assistants that take over in stop-and-go traffic, where speeds are so low that a worst-case collision would be a fender bender, it is conceivable that level-three automation will never happen.

COURTESY OF VOLVO CAR GROUP (1-3)

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NEXT YEAR Volvo Cars will field-test 100 vehicles equipped with systems that automate driving on special stretches of freeway (*1* and *2*). Volvos have also been used in European road-train tests (*3*).

And yet we will see highly automated cars soon, probably within the coming decade. Nearly every big automaker and many information technology companies are devoting serious resources to level-four automation: fully automated driving, restricted to specific environments, that does not rely on a fallible human for backup. When you limit the situations in which automated vehicle systems must operate, you greatly increase their feasibility. (Automated people movers have been operating in big airports for years—but they are on totally segregated tracks.)

In all probability, the next 10 years will bring automated valet-parking systems that will allow drivers to drop their cars at the entrance of a suitably equipped garage that excludes pedestrians and nonautomated vehicles. An onboard automation system will communicate with sensors placed throughout the garage to find out which parking spots are available and navigate to them. Because there will be no need to open the doors, parking spaces can be narrower than they are today, so more cars will be able to fit in garages in areas where space is expensive.

In urban pedestrian zones, business parks, university campuses and other places where high-speed vehicles can be excluded, low-speed passenger shuttles will operate without drivers. In such environments, limited-capability sensors should be adequate to detect pedestrians and bicyclists, and if a sensor detects a false positive and brakes unnecessarily, it will not harm anyone (although it will annoy the people in the vehicle). The CityMobil2 project of the European Commission has been demonstrating such technologies for several years and conducted its final demonstration in summer 2016.

Segregated bus ways and truck-only lanes will soon enable commercial vehicles to operate at higher levels of automation. Physically segregating these vehicles from other users will greatly simplify systems designed to detect and respond to threats. Eventually driverless trucks and buses will be able to follow a human-driven lead vehicle in fuel-saving platoons. Researchers worldwide, including the California Partners for Advanced Transportation Technology (PATH) program at the University of California, Berkeley, Japan's Energy ITS project, and the KONVOI and SARTRE projects in Europe, have already tested prototype bus- and truck-platoon systems.

Yet the most widespread implementation of level-four automation within the next decade will probably be automated freeway systems for personal passenger vehicles. These systems will permit automobiles to drive themselves under certain conditions on designated sections of freeway. The vehicles will have redundant components and subsystems so that if something goes wrong, they can "limp home" without human guidance. They will probably be restricted to fair weather on stretches of freeway that have been mapped in detail, down to the signage and lane markings. These sections of road might even have "safe harbor" locations where vehicles can go when they have problems. Most major vehicle manufacturers are hard at work developing these systems, and in 2017 Volvo Cars plans to conduct a public field test of such capabilities with 100 prototype vehicles in Gothenburg, Sweden.

These scenarios might not sound as futuristic as having your own personal electronic chauffeur, but they have the benefit of being possible—even inevitable—and soon. SA

Editor's note: *In September, U.S. federal regulators officially encouraged the development of driverless cars and released guidelines to govern their safety and technology. The industry has suffered some early setbacks, including two deaths in 2016 of passengers using the Autopilot feature in their Tesla vehicles.*

Steven E. Shladover helped to create in the 1980s the California Partners for Advanced Transportation Technology (PATH) program at the Institute of Transportation Studies at the University of California, Berkeley. He is a mechanical engineer by training, with bachelor's, master's and doctoral degrees from the Massachusetts Institute of Technology.

MORE TO EXPLORE

Technical Challenges for Fully Automated Driving Systems. Steven Shladover. Presented at the 21st World Congress on Intelligent Transport Systems, Detroit, Mich., September 7–11, 2014.

Towards Road Transport Automation: Opportunities in Public-Private Collaboration. Summary of the Third EU-U.S. Transportation Research Symposium, Washington, D.C., April 14–15, 2015. National Academies of Sciences, Engineering, and Medicine, 2015.

Summary of definitions for SAE International's 2016 report *Taxonomy and Definitions for Terms Related to On-Road Motor Vehicle Automated Driving Systems*: standards.sae.org/j3016_201609/

FROM OUR ARCHIVES

Driving toward Crashless Cars. Steven Ashley; December 2008.

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PHYSICS

ARE WE LIVING IN A COMPUTER SIMULATION?

Listen in as physicists and philosophers debate whether we are real or virtual

By Clara Moskowitz

MEDIOIMAGES Getty Images

If you, me and every person and thing in the cosmos were actually characters in some giant computer game, we would not necessarily know it. The idea that the universe is a simulation sounds more like the plot of *The Matrix,* but it is also a legitimate scientific hypothesis. Researchers pondered the controversial notion at the annual Isaac Asimov Memorial Debate in April 2016 at the American Museum of Natural History.

Moderator Neil deGrasse Tyson, director of the museum's Hayden Planetarium, put the odds at 50–50 that our entire existence is a program on someone else's hard drive. "I think the likelihood may be very high," he said. He noted the gap between human and chimpanzee intelligence, despite the fact that we share more than 98 percent of our DNA. Somewhere out there could be a being whose intelligence is that much greater than our own. "We would be drooling, blithering idiots in their presence," he said. "If that's the case, it is easy for me to imagine that everything in our lives is just a creation of some other entity for their entertainment."

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VIRTUAL MINDS

A POPULAR ARGUMENT for the simulation hypothesis came from University of Oxford philosopher Nick Bostrum in 2003, when he suggested that members of an advanced civilization with enormous computing power might decide to run simulations of their ancestors. They would probably have the ability to run many, many such simulations, to the point where the vast majority of minds would actually be artificial ones within such simulations, rather than the original ancestral minds. So simple statistics suggest it is much more likely that we are among the simulated minds.

And there are other reasons to think we might be virtual. For instance, the more we learn about the universe, the more it appears to be based on mathematical laws. Perhaps that is not a given but a function of the nature of the universe we are living in. "If I were a character in a computer game, I would also discover eventually that the rules seemed completely rigid and mathematical," said Max Tegmark, a cosmologist at the Massachusetts Institute of Technology. "That just reflects the computer code in which it was written."

Furthermore, ideas from information theory keep showing up in physics. "In my research I found this very strange thing," said James Gates, a theoretical physicist at the University of Maryland. "I was driven to error-correcting codes—they're what make browsers work. So why were they in the equations I was studying about quarks and electrons and supersymmetry? This brought me to the stark realization that I could no longer say people like Max are crazy."

ROOM FOR SKEPTICISM

YET NOT EVERYONE on the panel agreed with this reasoning. "If you're finding IT solutions to your problems, maybe it's just the fad of the moment," Tyson pointed out. "Kind of like if you're a hammer, every problem looks like a nail."

And the statistical argument that most minds in the future will turn out to be artificial rather than biological is also not a given, said Lisa Randall, a theoretical physicist at Harvard University. "It's just not based on well-defined probabilities. The argument says you'd have lots of things that want to simulate us. I actually have a problem with that. We mostly are interested in ourselves. I don't know why this higher species would want to simulate us." Randall admitted she did not quite understand why other scientists were even entertaining the notion that the universe is a simulation. "I actually am very interested in why so many people think it's an interesting question." She rated the chances that this idea turns out to be true "effectively zero."

"OUR CREATOR ISN'T ESPECIALLY SPOOKY, IT'S JUST SOME TEENAGE HACKER IN THE NEXT UNIVERSE UP."

—DAVID CHALMERS, *New York University*

Such existential-sounding hypotheses often tend to be essentially untestable, but some researchers think they could find experimental evidence that we are living in a computer game. One idea is that the programmers might cut corners to make the simulation easier to run. "If there is an underlying simulation of the universe that has the problem of finite computational resources, just as we do, then the laws of physics have to be put on a finite set of points in a finite volume," said Zohreh Davoudi, a physicist at M.I.T. "Then we go back and see what kind of signatures we find that tell us we started from non-continuous spacetime." That evidence might come, for example, in the form of an unusual distribution of energies among the cosmic rays hitting Earth that suggests spacetime is not continuous but made of discrete points. "That's the kind of evidence that would convince me as a physicist," Gates said. Yet proving the opposite—that the universe is real—might be harder. "You're not going to get proof that we're not in a simulation, because any evidence that we get could be simulated," said David Chalmers, a professor of philosophy at New York University.

LIFE, THE UNIVERSE AND EVERYTHING

IF IT TURNS OUT we really are living in a version of *The Matrix,* though—so what? "Maybe we're in a simulation, maybe we're not, but if we are, hey, it's not so bad," Chalmers said.

"My advice is to go out and do really interesting things," Tegmark said, "so the simulators don't shut you down."

But some were more contemplative, saying the possibility raises some weighty spiritual questions. "If the simulation hypothesis is valid, then we open the door to eternal life and resurrection and things that formally have been discussed in the realm of religion," Gates suggested. "The reason is quite simple: If we're programs in the computer, then as long as I have a computer that's not damaged, I can always rerun the program."

And if someone somewhere created our simulation, would that make this entity God? "We in this universe can create simulated worlds and there's nothing remotely spooky about that," Chalmers said. "Our creator isn't especially spooky, it's just some teenage hacker in the next universe up." Turn the tables, and we are essentially gods over our own computer creations. "We don't think of ourselves as deities when we program Mario, even though we have power over how high Mario jumps," Tyson said. "There's no reason to think they're all-powerful just because they control everything we do." And a simulated universe introduces another disturbing possibility. "What happens," Tyson said, "if there's a bug that crashes the entire program?" SA

Clara Moskowitz is *Scientific American*'s senior editor covering space and physics. She has a bachelor's degree in astronomy and physics from Wesleyan University and a graduate degree in science journalism from the University of California, Santa Cruz.

MORE TO EXPLORE

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FROM OUR ARCHIVES

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NEW VIEWS OF LIFE ON EARTH

For centuries, scientists have chronicled in exquisite detail how all kinds of species, from tiny bacteria to gigantic dinosaurs, spread across the planet and shaped its evolution. In 2016 researchers turned that focus to the human experience as well. Although textbooks often give a set explanation for how *Homo sapiens* populated the earth, new fossil discoveries are challenging those assumptions (*page 88*). Researchers are also documenting the incredible number of people who are fleeing their homelands because of violence and natural and man-made disasters. The migrations are so extensive that they are rapidly changing the makeup of nations (*page 98*). Investigators are also hotly debating whether we humans are transforming the earth's crust so extensively—by depositing layers of concrete, plastics, radiation and carbon—that we are ending a 12,000-year geologic epoch known as the Holocene and starting a totally new chapter called the Anthropocene (*page 104*).

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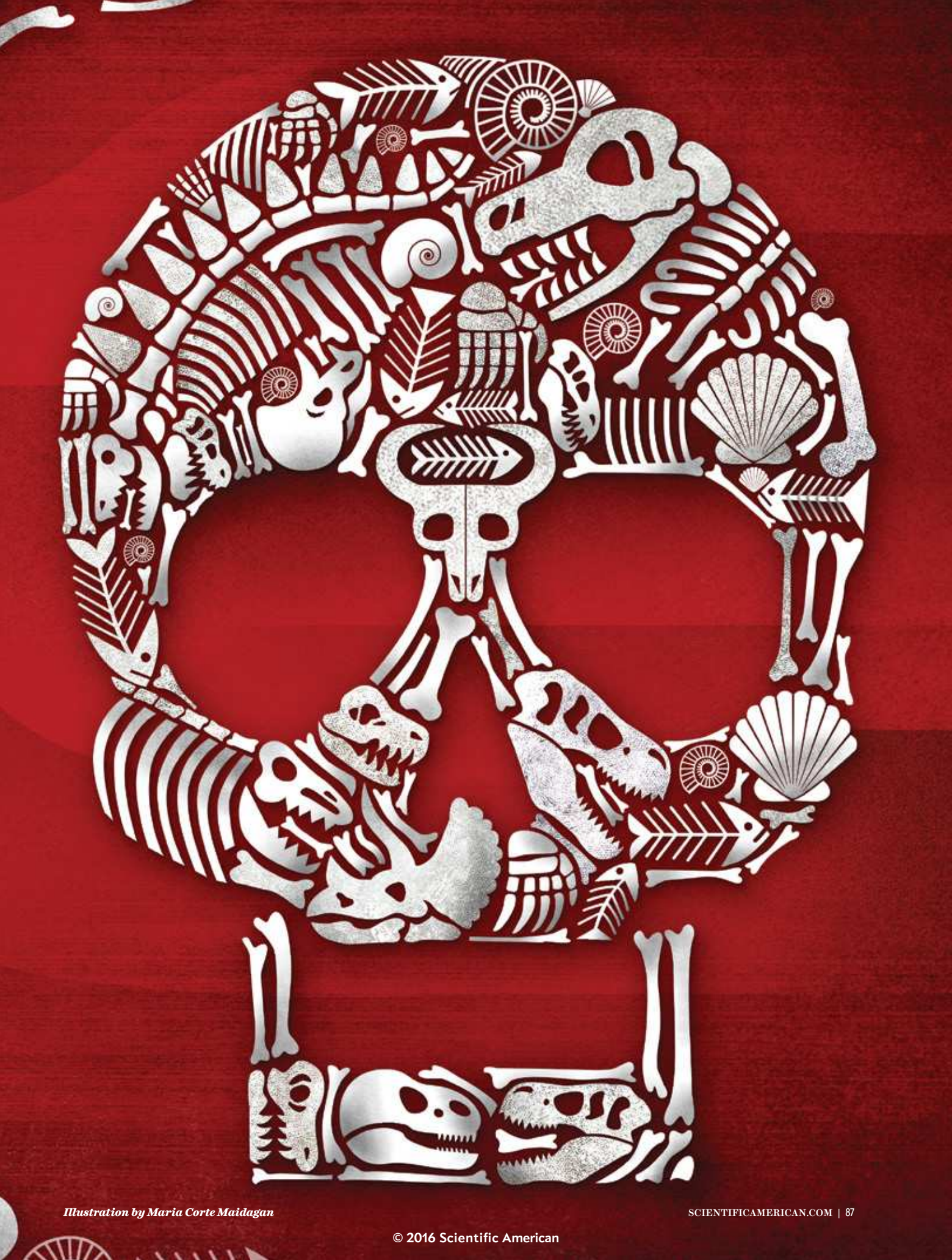

Illustration by Maria Corte Maidagan

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NEW HUMAN SPECIES: *Homo naledi* raises questions about the origin and evolution of our genus. In this replica of the composite skull, white areas indicate missing bone.

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Mystery Human

An astonishing trove of fossils has scientists, and the media, in a tizzy over our origins

By Kate Wong

IN BRIEF

In 2013 cavers discovered a cache of enigmatic fossils deep inside an underground cave system known as Rising Star near Johannesburg, South Africa.

Over the course of two expeditions scientists recovered more than 1,550 specimens belonging to at least 15 individuals from the site.

In September 2015 researchers unveiled the discovery to great fanfare, announcing that the bones represent a new species, *Homo naledi*, that calls into question long-standing ideas about the rise of *Homo*.

Critics have raised concerns about the recovery and analysis of the fossils.

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IN THE BRAND-NEW FOSSIL VAULT AT THE UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG, in South Africa, shelf space is already running out. The glass-doored cabinets lining the room brim with bones of early human relatives found over the past 92 years in the many caves of the famed Cradle of Humankind region, just 40 kilometers northwest of here. The country's store of extinct humans has long ranked among the most extensive collections in the world. But recently its holdings doubled with the discovery of hundreds of specimens in a cave system known as Rising Star. According to paleoanthropologist Lee Berger and his colleagues, who unearthed and analyzed the remains, they represent a new species of human—*Homo naledi,* for "star" in the local Sotho language—that could overturn some deeply entrenched ideas about the origin and evolution of our genus, *Homo.*

Berger is camera-ready in a brown leather blazer and set to give his spiel to the dozen or so journalists, including me, gathered around him in the vault in late 2015. He directs the visitors' attention to the six black carrying cases—originally made to hold assault rifles—arrayed on tables around the room. Each contains a dizzying assortment of fossils nestled in its foam-lined interior. In the cabinets along the back wall, more *H. naledi* bones fill dozens of clear plastic containers labeled "cranial fragments," "pelvis," "radius." Berger reaches into case number two, which holds the crown jewels of the Rising Star assemblage—the group of bones that defines the species—and lifts out an upper jaw and a lower jaw. He carefully holds them one atop the other and displays the matched pair with a practiced flourish so that everyone gets a good look. The crowd murmurs appreciatively, pens scribble, camera shutters click, flashes pop. And he glides on to the next specimen, fielding questions, posing for photographs and encouraging the visitors to snap selfies with the vault's celebrity charges.

Just a few decades ago the sum total of fossils belonging to our extinct human relatives, also called hominins, could fit in a desk drawer. Those destitute days are long gone. Scientists have since amassed more evidence of the evolutionary history of the human family than of many other animal groups, including our closest living relatives, the great apes. As a result, they now know, for example, that humanity's roots reach back at least seven million years and that for much of that time our ancestors shared the planet with other hominins.

Yet they still have much to learn. Some chapters of the human story are completely unknown from the fossil record; others have been drafted on the basis of evidence so scanty that they are little more than speculation. And so even though the fossil record of humans is vastly bigger than it once was, it is still imperfect enough that new discoveries often alter scientists' understanding of the details of humanity's past—sometimes significantly so.

The Rising Star fossils are the latest to rock the paleoanthropology establishment. Berger and his team argue that *H. naledi* could illuminate the long-sought roots of *Homo* and revamp the human family tree. What is more, the researchers suggest, this creature, which had a brain the size of an orange, engaged in ritual behavior previously attributed exclusively to much brainier hominins—a finding that could upend the prevailing wisdom linking cognitive sophistication to large brain size.

HOLE IN THE GROUND: Fossils of *Homo naledi* were found in a cave in South Africa's Cradle of Humankind.

Some critics have dismissed these claims outright. Others have greeted them with uncharacteristic reticence. One major stumbling point for many is that the age of the bones is unknown. They could be more than four million years old or less than 100,000 years old. The lack of a date is not the only concern weighing on outside observers, however. The way the fossils were unearthed, analyzed and revealed to the rest of the world has vexed some of the field's leading scholars, who charge that Berger and his colleagues rushed the job and prioritized publicity over

PAGE 88: COURTESY OF JOHN HAWKS AND UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG; RECONSTRUCTION BY PETER SCHMID *University of the Witwatersrand*; THIS PAGE: COURTESY OF MARINA ELLIOTT *University of the Witwatersrand*

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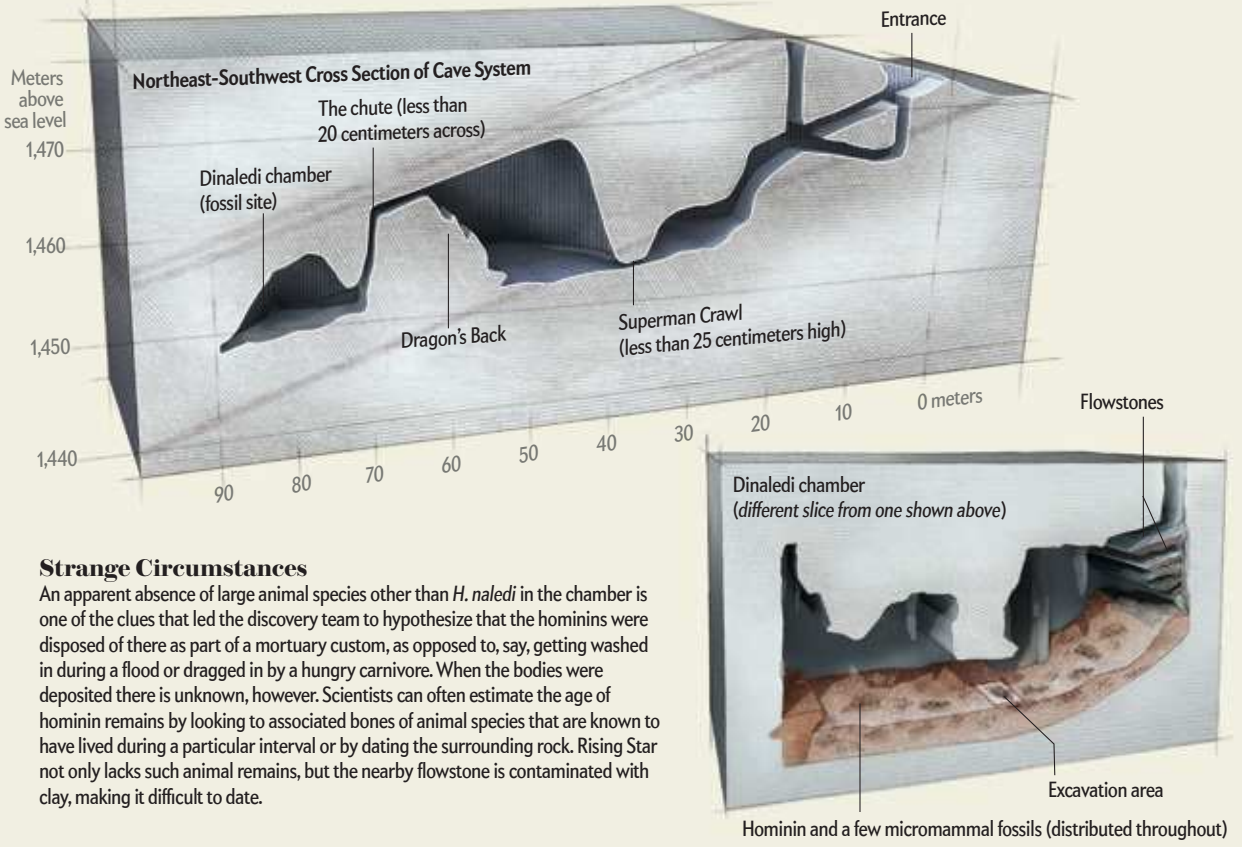
LOCATION

Chamber of Bones

Cavers discovered the fossils of the new human species *Homo naledi* in an underground cave known as Rising Star, just outside Johannesburg, South Africa (*right*). The bones come from the so-called Dinaledi chamber, which sits 30 meters below the surface. To reach it, excavators had to undertake steep climbs and squeeze through tight passages (*below*). *H. naledi* may have taken similar pains to get there: researchers think it may have been intentionally disposing of its dead in the chamber (*inset*), and although geologists are still working to understand how the cave evolved over time, they have yet to identify other plausible routes into the chamber.



Strange Circumstances

An apparent absence of large animal species other than *H. naledi* in the chamber is one of the clues that led the discovery team to hypothesize that the hominins were disposed of there as part of a mortuary custom, as opposed to, say, getting washed in during a flood or dragged in by a hungry carnivore. When the bodies were deposited there is unknown, however. Scientists can often estimate the age of hominin remains by looking to associated bones of animal species that are known to have lived during a particular interval or by dating the surrounding rock. Rising Star not only lacks such animal remains, but the nearby flowstone is contaminated with clay, making it difficult to date.

SOURCE: "GEOLOGICAL AND TAPHONOMIC CONTEXT FOR THE NEW HOMININ SPECIES *HOMO NALEDI* FROM THE DINALEDI CHAMBER, SOUTH AFRICA," BY PAUL H.G.M. DIRKS ET AL., IN *ELIFE*, ARTICLE NO. 09561; PUBLISHED ONLINE SEPTEMBER 10, 2015

science. In a field known for its fierce rivalries, heated debate over new finds is the norm. But there is more on the line in the row over the Rising Star remains than a few egos. How scientists respond to this discovery in the longer term could set a new course in the quest for human origins, changing not only the questions they ask but the ways in which they attempt to answer them.

INTO THE DEEP

IN A WAY, it was a set of grainy photographs shown to Berger on October 1, 2013, that sparked this spectacle. Berger had hired geologist Pedro Boshoff to search the Cradle for new hominin sites. Over the years miners and fossil hunters had combed the region many times over. But Berger had good reason to think there was more to find. Five years earlier his then nine-year-old son had stumbled across bones of a previously unknown member of the human family, *Australopithecus sediba,* right in the middle of the Cradle.

Now Boshoff and local cavers Rick Hunter and Steven Tucker had found what appeared to be human bones littering the floor of an extremely difficult-to-reach chamber 30 meters down in the Rising Star cave system, just a few kilometers from the spot where Berger and his son had found *A. sediba*. The explorers had not collected any of the material, but they had taken pictures. As soon as Berger saw them, he knew the bones were important. They had features that clearly differed from those of anatomically modern humans—*Homo sapiens*. And there were lots of them, enough to represent a skeleton.

Berger immediately began making plans to recover the remains. There was a problem, though. He was not going to be able to collect them himself. The route from the cave entrance to the chamber that held the bones contained passages far too narrow to accommodate Berger's broad frame or that of most of his scientist colleagues for that matter. Widening these passages would disrupt the integrity of the cave and possibly damage the bones—

Illustration by José Miguel Mayo

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a nonstarter, as far as he was concerned. So he put out a call on Facebook for skinny scientists who had experience caving and excavating old remains and who could come to Johannesburg on short notice to mount an expedition in exchange for little more than a plane ticket and the promise of adventure.

Five weeks after Boshoff showed him the tantalizing photographs, Berger had selected his team of excavators—all women, coincidentally—to carry out the difficult, dangerous work of recovering the bones from the chamber, as well as a crew to support the team's efforts; he developed a protocol for collecting the material and documenting exactly where in the chamber each piece of bone came from; and he established a group of senior scientists to oversee the excavation via closed-circuit television and to identify, log and store the specimens as they came out. He also had a plan for how to publicize the endeavor—a full-bore media blitz, carried out in partnership with *National Geographic* and *NOVA,* that would include live tweets and daily blogs, radio interviews and video clips posted from the field, as well as a TV documentary that would air at a later date, after the remains were eventually published. On November 10, cameras rolling, the excavators crawled, climbed and wriggled their way into the pitch-dark chamber and began the recovery effort.

Marina Elliott was the first scientist to enter the chamber. "I didn't know what to expect, but I was excited," she recalls when I accompany her to the Rising Star site. It is high noon on a bright, hot austral summer's day, and outside the cave the wind carries the sound of cars whizzing past on the nearby freeway. But inside the cave it is dim and cool and hushed—the stillness of age. A shaft of light from a natural opening in the ground above bathes the craggy interior, giving it the air of a place of worship.

The serenity of this part of the cave belies the danger farther in, however. Elliott shines her flashlight down one of the corridors, illuminating a perforated curtain of limestone. Behind that wall lies the first of the squeeze points on the route into the fossil chamber, she explains—the Superman Crawl, a tunnel that the women had to negotiate belly to ground and one arm outstretched. The journey did not get easier from there. A jagged ridge called the Dragon's Back loomed ahead, followed by a 12-meter-long, vertical chute less than 20 centimeters (eight inches) across that opened into the chamber of bones.

But their efforts were richly rewarded. There were bones everywhere—much more than the single skeleton Berger had expected to salvage. Over the next 21 days Elliott and her colleagues hauled out 1,200 specimens. A second, shorter expedition in March 2014 yielded several hundred more. In total, the team recovered more than 1,550 bones and bone fragments of at least 15 individuals—including infants, tweens, young adults and old-timers—from an area the size of a card table. All told it is one of the largest single assemblages of hominin fossils ever found. And the team only scratched the surface. More bones, possibly thousands more, remain in the chamber.

A STAR IS BORN

WITH SAFE AFTER SAFE stuffed with hominin fossils, Berger and his colleagues now faced the daunting prospect of assessing them. Even before the researchers began their formal assessment, while the bones were still coming out of the ground, the find had an air of mystery about it. For one thing, the bones appeared to have a weird combination of primitive and modern traits. For another, no animal remains apart from those of a few small birds and rodents had turned up in the chamber along with the hominin bones. Larger animals such as monkeys, antelopes and hyenas almost always accompany hominin fossils, particularly those found in underground caves. The absence of such species at Rising Star demanded explanation.

Berger recruited an army of 35 early-career researchers to help describe the fossils over the course of a monthlong workshop in Johannesburg in May 2014. For most of these people—many still working on their Ph.D.s—it was a rare opportunity to work on new fossils, as opposed to studying material that had already been characterized by other, more seasoned scientists. They worked in groups organized by body part: skull, hand, teeth, spine, hip, leg, foot, and so forth. When they pooled their findings, a startling picture emerged of a tall, slender hominin with upper limbs built for climbing and using tools, lower limbs built for upright striding and a teeny brain. It is "a really, really strange creature," Berger says.

COURTESY OF JOHN HAWKS AND UNIVERSITY OF THE WITWATERSRAND

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HEAD TO TOE: Vast Rising Star fossil assemblage includes rare foot bones (*1*) and multiple leg bones (*2*). Though fragmentary, the fossils are beautifully preserved and can in some instances be attributed to the same individual, as is the case for the lower jaw (*3*) and skull fragments (*4*).

On a Friday afternoon in December 2015, senior team member John Hawks of the University of Wisconsin–Madison takes me back to the vault to point out some of the salient aspects of the Rising Star remains. The rest of his colleagues are still outside enjoying beer and barbecue at the department holiday party, but Hawks is in his element here among the bones. He bustles around the room, setting the fossil cases out on the tables and selecting replicas of other hominin specimens from the vault's vast collection for comparison.

The skull exhibits a mishmash of traits associated with various hominin species. It would have held a brain measuring just 450 to 550 cubic centimeters—as small as that of primitive *Australopithecus afarensis,* best known from the 3.2-million-year-old Lucy skeleton, found in 1974 in Ethiopia. Yet the shape of the skull evokes the more humanlike *Homo erectus*. The teeth resemble those of *Homo habilis,* one of the most primitive members of our genus, in the way they increase in size from the front of the tooth row to the back. But overall the teeth are small, and the molars have simple crowns with fewer, lower cusps—traits associated with later *Homo*.

The bones below the head echo the mix-and-match theme. The upper limb pairs a shoulder and fingers adapted to climbing with a wrist and palm built for manipulating stone tools—an activity that was not thought to become important to hominins until after they had abandoned life in the trees and evolved large, inventive brains. And the lower limb marries a Lucy-like hip joint to a foot that is virtually indistinguishable from our own. Researchers have been operating under the assumption that the signature features of *Homo*—such as a toolmaking hand, big brain and small teeth—evolved in concert. "*Sediba* and *naledi* show that things we thought we evolved together did not," Hawks asserts. (Like *H. naledi, A. sediba* displays a startling mix of traits.)

This unprecedented combination of primitive and modern features is not the only distinctive thing about *H. naledi*. The fossils also have traits never before seen in a member of the human family. Hawks plucks one of the finger bones out of its foam cutout. It is the first metacarpal, the bone in the palm that sits below the thumb, and when he displays it next to the same bone from *H. sapiens,* the difference is stark. The shaft of its first metacarpal is smooth, thick and broad for its entire length. *H. naledi*'s, in contrast, is narrow at the base and broad at the top, with a sharp crest running along its shaft and thin wings of bone on the sides. The femur bears unique traits, too, as do other elements.

To Berger and his colleagues, the novel combination of australopithecine and *Homo* characteristics, along with the presence of unique traits, easily justified assigning the Rising Star fossils to a new hominin species. Although the researchers have yet to establish the age of the fossils, in one of two papers announcing the find, published in September 2015 in the online open-access journal eLife, they proposed that, given its primitive features compared with early *Homo* species such as *H. habilis* and *H. erectus, H. naledi* might be older than two million years and stem from the base of the genus *Homo*. If so, the discovery would be a major coup: the origin of *Homo* is arguably the biggest unsolved mystery in all of human evolution because fossils transitional between the australopithecines, with their many apelike traits, and later *Homo,* with its modern body plan, are exceedingly rare and mostly scraps. Scientists have been eager to elucidate which hominin species founded the *Homo* branch of the hominin family tree and how the traits in the modern human body plan evolved with new discoveries.

Berger's team did not stop at saying the find could bear on the origin of *Homo,* however. It argued that the unexpected mix of traits evident in *H. naledi* implies that isolated fragments cannot be used to understand the evolutionary relationships of fossil humans, because the part cannot predict the whole—fighting words to those researchers who have interpreted isolated bones as the earliest evidence of the *Homo* lineage.

Perhaps even more provocative than the team's ideas about what *H. naledi* means for understanding hominin relationships is how it interpreted *H. naledi*'s behavior. In their attempts to figure out how the hominins ended up in the chamber, the re-

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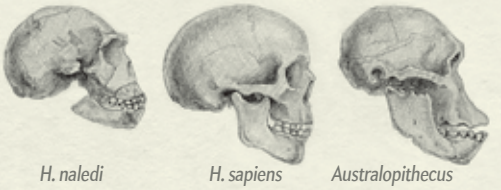
A Novel Mix

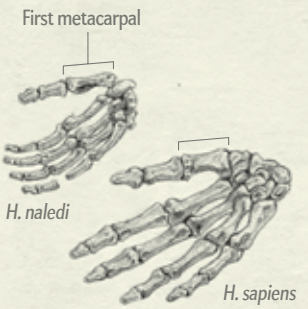
The excavations at Rising Star have yielded more than 1,550 fossil specimens of *Homo naledi* belonging to at least 15 individuals ranging from infants to oldsters. Nearly every bone in the body is represented in the collection, many of them more than once. From these remains scientists have reconstructed a creature with a startling combination of traits associated with the primitive australopithecines and traits seen in various species in our genus, *Homo*, as well as some traits not known from any other hominin species. Examples of these features are highlighted in the diagram below.



Skull of *H. naledi* housed a brain as small as 450 cubic centimeters—a size that is typical for australopithecines but significantly smaller than the brains of *H. sapiens* and most other members of *Homo*.

Teeth are primitive in the way they increase in size from front to back. Overall they are small, and the molars have comparatively simple cusps—both traits of later *Homo* species.

Shoulder socket faces up like an ape's or australopithecine's rather than out to the side like ours does. This upward orientation is an adaptation to climbing trees.

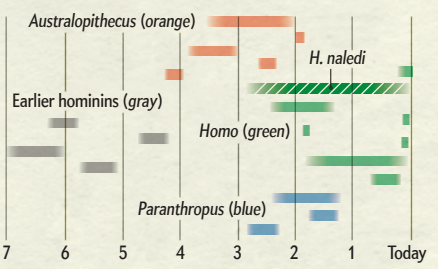


Femur has a small head and long neck compared with the large head and small neck seen in the *Homo sapiens* femur. These features suggest that *H. naledi*'s hip worked like an australopithecine's.

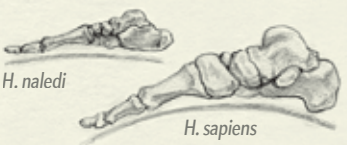
Hand has strongly curved fingers, suggesting that *H. naledi* climbed in trees. Yet the wrist and palm look modern and appear to be adapted to manipulating tools. For its part *H. naledi*'s first metacarpal, the bone in the palm below the lowermost thumb bone, looks neither *Homo*-like nor *Australopithecus*-like and is utterly unique.

A New Twig in Our Tree

The discovery team argues that *H. naledi*'s particular mix of characteristics suggests that the species originated close to the origin of *Homo*—a coveted spot in the family tree. But *H. naledi* preserves parts of the anatomy that are not known for other early *Homo* species, complicating efforts to understand how these extinct hominins are related to one another—and to us.



Foot is remarkably like our own, apart from the slightly curved toes and somewhat lower arch, and thus well adapted to upright striding. But the combination of this modern foot and the primitive hip means *H. naledi* would have walked differently from us.



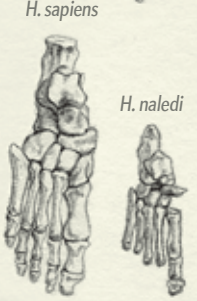


Illustration by Portia Sloan Rollings, Graphic by Jen Christiansen

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searchers considered a number of mechanisms known to account for hominin accumulations at other sites, including the possibility that their bones had washed into the cave system during a flood or that large carnivores had dragged them there to eat. Yet the available evidence did not match any of those explanations. Floodwaters, for instance, would have surely carried the remains of other animals into the chamber, too. And carnivores would have left behind telltale tooth marks on the bones. All things considered, the team concluded, the likeliest explanation was that *H. naledi* had intentionally deposited the bodies in the chamber.

The hominins would have had to go to considerable lengths to do so. Although the team geologists do not yet know exactly how the Rising Star cave system formed and changed over time, they have found only one entrance to the bone chamber—the one the excavators squeezed through to recover the fossils. If that was indeed the only entrance, then whoever disposed of the dead would have had to, at minimum, scale the 20-meter spine of the Dragon's Back to reach the opening of the chute that opens into the chamber. From there they could have either crawled down the chute with the bodies or just dumped them in and let them slide into the chamber below. And if the route into the chamber was always pitch-dark, as the team thinks it was, then the hominins may have required an artificial light source to find their way in. The suggestion was that tiny-brained *H. naledi* not only had a mortuary ritual but mastery of fire.

Ensconced in a leather club chair in the sitting area of his office, coffee mug in hand, Berger launches into a discussion of what the Rising Star find means for human evolution. It's 7:30 in the morning, but the blinds are drawn, and the lights are low. Between the animal hide rugs decorating the floor and the jazz warbling from a vintage-style turntable, the room feels more like a gentleman's hunting lodge than a work space. "There is no age at which [the find] is not disruptive," he exults. If it is old, then critical physical and behavioral traits may have emerged at the root of our genus or earlier, rather than in later *Homo*. Really old *H. naledi* could even oust the australopithecines from the line leading to us, according to Berger. If, on the other hand, the fossils are young, researchers are going to have to reconsider which species left behind the cultural remains at key archaeological sites across Africa.

It may be *H. naledi* originated millions of years ago and managed to persist across the ages unchanged, like a coelacanth, overlapping with other *Homo* species, including *H. sapiens,* for a time. Perhaps it invented some of the cultural traditions archaeologists have traditionally assumed originated with our kind, Berger says. Possibly *H. naledi* interbred with our ancestors and contributed DNA to the modern human gene pool, like Neandertals and Denisovans did.

CASTING ASPERSIONS

WHEN THE TEAM announced its discovery in eLife in 2015, the world went wild for *H. naledi*. Seemingly every media outlet on the planet covered the find. Even the *Onion* joined the bandwagon, running a doctored image of a lachrymal Berger with a story entitled "Tearful Anthropologists Discover Dead Ancestor of Humans 100,000 Years Too Late." Yet underneath that tidal wave of public enthusiasm runs a current of discontent among some of paleoanthropology's elite. No one disputes that the find is important—a cave full of human fossils is extraordinary—but the team's approach to recovering, describing and interpreting the bones has raised eyebrows.

Berger is no stranger to side eye from his academic peers. Telegenic and silver-tongued, he hooked up with *National Geographic* early in his career. The relationship brought research funding, bylines and television appearances. Yet he had found few fossils, and his scientific papers and popular writings met with accusations of sloppy scholarship and grandstanding from some of paleoanthropology's most respected figures, including Tim White of the University of California, Berkeley, and Bernard Wood of George Washington University.

Berger's discovery of *A. sediba* in 2008 raised his scientific profile. Even his harshest critics conceded that the find, which included two largely complete skeletons dated to 1.98 million years ago, was spectacular. But many did not agree with his interpretation of it. Berger had long contended that South Africa was being overlooked in favor of East Africa in the search for *Homo*'s origin. *A. sediba,* with a mosaic of australopithecine and *Homo* traits, seemed to offer a means of potentially rooting *Homo* in South Africa. The problem was that the oldest fossils attributed to *Homo* were East African specimens older than *A. sediba*. Berger argued that fossil fragments like the ones from East Africa that were being held up as the earliest *Homo* could no longer be assigned to one taxon or another because his skeletons, with their surprising combination of traits, showed the whole was not inferable from the part. His peers largely rejected that claim.

With *H. naledi,* Berger doubled down on the public outreach and on those controversial ideas about *Homo*'s origin and fragmentary fossils. It did not take critics long to loose their arrows. White told his university's alumni association magazine, *California,* that the Rising Star fossils looked like primitive *H. erectus,* not a new species. White is best known for his discoveries of hominin fossils in Ethiopia, including those of 2.4-million-year-old *Australopithecus garhi,* which he and Berhane Asfaw of the Rift Valley Research Service and their colleagues said were from the right time and place to be ancestral to *Homo.* He further accused the Rising Star team of damaging fossils during excavation and rushing its findings to publication. Later, in a scathing blog post for the *Guardian,* White warned of the dangers of mixing science and showmanship. "We are witnessing portions of science collapsing into the entertainment industry," he wrote.

White is not the only one with concerns. Carol Ward of the University of Missouri cautions that although the quantity of fossils is stunning, their significance remains unknown. She emphasizes the importance of determining the age of the bones: "When we know how old they are, then we can tell you what they mean for human evolution but not until then."

Ward also has misgivings about the paper describing the fossils, noting that it did not include sufficient data about how they compare with other relevant fossils for outside scientists to be able to evaluate many of the team's claims. Nor did the paper contain a phylogenetic analysis—basically a study in which a computer program compares traits across a group of organisms and thereby reconstructs the members' evolutionary relationships—which could reveal where *H. naledi* fits in the human family tree. "There seems to be a great desire [on the part of the authors] for it to be related to the origins of *Homo,*" she observes, but in the absence of a detailed phylogeny or a date, no one can know if it is.

Many researchers stand by the thinking that, based on present

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evidence, *Homo* debuted in East Africa. In 2015, months before the details of *H. naledi* were released, Brian Villmoare of the University of Nevada, Las Vegas, Kaye Reed of Arizona State University and their colleagues announced their discovery of a 2.8-million-year-old piece of lower jaw from the site of Ledi-Geraru in northeastern Ethiopia that they say is the earliest known representative of our genus. The jaw has clear hallmarks of *Homo,* they observe, as well as traits transitional between *Australopithecus* and *Homo.* Without a date, the *H. naledi* fossils cannot unseat the Ledi-Geraru jaw as the oldest evidence of our lineage, in Reed's view, nor does she accept the argument made by Berger, Hawks and their colleagues that isolated fragments of anatomy cannot be reliably assigned to one taxonomic group or another. "I have a good date at 2.8, and there are features of *Homo,*" she maintains.

Paleoanthropologists disagree on which fossils herald the dawn of *Homo* partly because they are divided over what constitutes *Homo. H. naledi* "highlights an ongoing debate about how to define *Homo,* both for things we have pieces of and things we have more of," comments Susan Antón of New York University, an expert on early members of our genus. Sorting *Homo* from *Australopithecus* is "a very messy thing for everyone right now, and different people have different philosophies about how to make that distinction." She and her collaborators have been defining it on the basis of traits found in the cranium, jaws and teeth. Others have argued that the distinction between the two has to be based on the bones below the head—the postcrania, as they are termed—because they reflect the major adaptive changes hominins underwent as they transitioned from wooded environments to open ones. But those postcranial bones are largely unknown for early *Homo* species. The Rising Star fossils are "an embarrassment of riches," Antón remarks. But the mosaic of traits gives mixed signals, and Berger's team did not explicitly state how it defines *Homo* and why. "We have a lot more talking to do," she says of the field.

Yet even if the Rising Star remains do constitute a new *Homo* species and even if they turn out to be more than two million years old, those facts alone may not be enough to sway the skeptics toward the notion that *H. naledi* was on or near the line leading to us. George Washington's Wood suspects that the bones represent a relic population that might have evolved its odd traits in relative isolation. "South Africa is a cul-de-sac at the bottom of the African continent," he says. "My guess is gene exchange in this cul-de-sac was probably not as common as it was in East Africa, where you have a lot more potential for homogenization, with genes coming in from southern and central Africa." Wood points to another weird species of *Homo*—the small-brained, small-bodied *Homo floresiensis* that persisted on the island of Flores in Indonesia long after *H. sapiens* originated in Africa—as another example of such a relic population.

The suggestion that small-brained *H. naledi* was ritually disposing of its dead has likewise met with resistance. "It would be quite radical," says archaeologist Alison Brooks of George Washington University. The practice is widely thought to be exclusive to the much larger-brained anatomically modern humans and possibly Neandertals and only became commonplace after 100,000 years ago. "I don't want to rule it out entirely that [the Rising Star researchers] are right," Brooks adds, "but I just think it is so far out there that they really need a higher standard of proof."

GETTING A GRIP: Hand of *H. naledi* is the most complete one known for an extinct human species.

In fact, some of the discovery team members themselves struggled with the idea that *H. naledi* was deliberately disposing of its dead in that underground chamber, if only for logistical reasons. "It's hard to get in there with my backpack, never mind dragging a body," Elliott reflects. "But we spent two years trying to find an alternative and couldn't."

The debate over how the bones got into the remote chamber intensified in April 2016, when Aurore Val of the University of the Witwatersrand published a critique of the team's interpretation in the *Journal of Human Evolution*. In it, Val, who is not on Berger's team but was his graduate student, argued that because caves can evolve considerably over time, it is impossible to say what Rising Star was like when the fossils landed in the chamber without knowing the age of the bones—there might have been an easier way in. She further contends that the researchers did not study enough of the fossil remains from the site to exclude the possibility that water or carnivore activity played a role in accumulating the bones there.

EYE ON THE PRIZE

BERGER DISMISSES THE DETRACTORS. Staunchly defending the care with which the team excavated the fossils, he explained in a public post on Facebook that the damage on the bones was already there when Rising Star team members first arrived on the scene. Berger presumes it resulted from unknown amateur cavers who had explored the chamber before them and stepped on the bones. The excavators were able to work quickly, he says, because "we didn't have a lot of problems other teams have." At other sites, fossils are typically encased in rock. Excavation and cleaning of such fossils are typically extremely laborious and time-consuming. But at Rising Star the fossils were simply lying in damp earth that

COURTESY OF JOHN HAWKS AND UNIVERSITY OF THE WITWATERSRAND

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brushed away easily. And unlike other teams, which are small and conduct their research in distant locales six to eight weeks a year, Berger's is large and based in Johannesburg, so it can work at the site or in the vault any time. If you look at the Rising Star work in terms of person-hours logged in the time between discovery and publication, "it's as much as anyone else has done," he insists.

As for White's suggestion that the fossils belong to primitive *H. erectus,* not a new species, "he disagrees with everything except the ones he basically has named," Berger quips. Assigning the *naledi* remains to *H. erectus* would mean that *erectus* had more variation than is seen in our own species, which is improbable, in his view. More to the point, *H. naledi* has unique traits not seen in any other hominin. "If we're going to be evolutionary biologists, the argument stops there," Berger declares. "Frankly I'm surprised [people] aren't arguing that it's a new genus," rather than merely a new species.

Asked about dating the Rising Star fossils, Berger says the geologists are working on it and will get the timing down eventually. But he maintains that the date will not change their understanding of how *H. naledi* is related to other members of the human family. Although *H. naledi* has some key traits of *Homo,* the overall package is in some ways more primitive than that of *H. habilis* and, for that matter, that of the Ledi-Geraru jaw that currently holds the title of oldest *Homo* fossil. No matter what age the Rising Star fossils turn out to be, they imply that *H. naledi*'s branch of the family tree sprouted before these other branches did. If the fossils are young, then they represent a late population of this species.

Why, then, didn't the team include a phylogeny in the paper announcing the fossils as a new species? To figure out how organisms are related to one another, evolutionary biologists use a method called cladistics that sorts taxa into groups based on novel characteristics they share with their last common ancestor but not earlier ones. The catch is, the method works best when the characteristics are observable in all the organisms in question.

Where fossils are concerned, meeting that requirement is easier said than done because they vary widely in the traits they preserve. In paleoanthropology, researchers have tended to base their cladistic analyses on traits found in skulls and teeth: skulls because they vary widely in form in hominins and thus historically were thought to be particularly useful for defining species and teeth because they are the most common elements in the hominin fossil record. Bones from the rest of the skeleton are not always found in association with skulls or teeth, so it can be difficult to assign them to a species that is defined by cranial or dental remains. Moreover, a skeletal element that is known in one species is often missing in another.

Indeed, some of *H. naledi*'s key elements—including its nearly complete sets of hand and foot bones—are only partly represented in the fossil record of other *Homo* species, such as *H. erectus* and *H. habilis,* if they are even represented at all. Lacking corresponding parts with which to compare them, the researchers could not conduct a cladistic analysis of *H. naledi* that factored in its many postcranial traits of interest. With that course of comparison closed off to them, the researchers ran an analysis based on skull and dental traits. But some of the test results did not make logical sense, suggesting that *H. naledi,* with its many primitive traits, is more closely related to *H. sapiens* than to the much older *H. erectus*. To Berger, that finding underscores that trees based on data from one anatomical region, such as the head or teeth, are unreliable. (In a paper published in the August 2016 *Journal of Human Evolution,* Mana Dembo of Simon Fraser University in British Columbia and her colleagues reported that a statistical analysis of the *H. naledi* skull and tooth remains supported the link to *Homo* but suggested a considerably younger age of 912,000 years.)

Berger remains certain that *H. naledi* will shake up scientists' understanding of human evolution one way or another. But he is not asking his peers to take his word for it. In a departure from the usual way of doing things in paleoanthropology, which has a reputation for secrecy where access to fossils is concerned, he instituted an explicit policy for the Rising Star remains that makes them available to any researcher who applies to see them. And on the day they published the eLife papers, the researchers released free three-dimensional scans of critical bones on MorphoSource, a digital repository for anatomical data, allowing visitors to print their own 3-D replicas of the specimens. The data resolution is not yet high enough for the purposes of carrying out original research, but "it's good enough to check what we're saying," Berger says.

"It's such an overwhelming positive that people are getting access; the complaints are just noise," observes David Strait of Washington University in St. Louis. He notes that in 2000, White wrote a prominent editorial in which he asserted that, given the intense public interest in human origins, paleoanthropologists have a special duty to get things right. "That's completely wrong," Strait asserts. "Of course, we should try to do things well, but science should operate by falsifying possibilities. We narrow down the possible truths to get a better idea of what happened in the past, and there is always the possibility for new data to emerge that change everyone's thinking." By making the fossils available to other researchers, Strait says, Berger has given those scientists who disagree with him an avenue to test their ideas against his: "The field moves forward only if people can study the stuff."

In the meantime, with or without the opposition's approval, work will continue apace at Rising Star. The geologists are reconstructing the history of the cave, the excavators are recovering more fossils from the chamber, the molecular biologists will attempt to extract DNA from the bones. And the fossil hunters are seeking new leads. "[*H. naledi*] should launch the greatest age of exploration there ever was," Berger declares with characteristic zeal. If it doesn't, maybe the team's next find will: he reveals that his explorers have already made progress on that front. Pressed for more detail, Berger demurs, other than to say with a sly grin that they have located "more than one" new site that has set his heart to racing like Rising Star did when he first saw those grainy photographs. The show will go on. SA

Kate Wong is a senior editor at *Scientific American.*

MORE TO EXPLORE

Geological and Taphonomic Context for the New Hominin Species *Homo naledi* from the Dinaledi Chamber, South Africa. Paul H.G.M. Dirks et al. in eLife, Article No. 09561. Published online September 10, 2015.

***Homo naledi*, a New Species of the Genus *Homo* from the Dinaledi Chamber, South Africa.** Lee R. Berger et al. in eLife, Article No. 09560. Published online September 10, 2015.

FROM OUR ARCHIVES

First of Our Kind. Kate Wong; April 2012.

scientificamerican.com/magazine/sa

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SYRIAN MAN comforts his wife after a treacherous, 16-kilometer ocean crossing in an overcrowded raft from Turkey to Greece, an escape route for many people leaving war-torn Syria.

Photographs by John Wendle

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SUSTAINABILITY

Syria's Climate Refugees

Farmers who have escaped the embattled nation explain how drought and government abuse have driven social violence

By John Wendle

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KEMAL ALI RAN A SUCCESSFUL WELL-DIGGING BUSINESS FOR FARMERS IN northern Syria for 30 years. He had everything he needed for the job: a heavy driver to pound pipe into the ground, a battered but reliable truck to carry his machinery, a willing crew of young men to do the grunt work. More than that, he had a sharp sense of where to dig, as well as trusted contacts in local government on whom he could count to look the other way if he bent the rules. Then things changed. In the winter of 2006–2007, the water table began sinking like never before.

Ali had a problem. "Before the drought I would have to dig 60 or 70 meters to find water," he recalls. "Then I had to dig 100 to 200 meters. Then, when the drought hit very strongly, I had to dig 500 meters. The deepest I ever had to dig was 700 meters. The water kept dropping and dropping." From that winter through 2010, Syria suffered its most devastating drought on record. Ali's business disappeared. He tried to find work but could not. Social uprisings in the country began to escalate. He was almost killed by cross fire. Now Ali sits in a wheelchair at a camp for wounded and ill refugees on the Greek island of Lesbos.

Climatologists say Syria is a grim preview of what could be in store for the larger Middle East, the Mediterranean and other parts of the world. The drought, they maintain, was exacerbated by climate change. The Fertile Crescent—the birthplace of agriculture some 12,000 years ago—is drying out. Syria's drought has destroyed crops, killed livestock and displaced as many as 1.5 million Syrian farmers. In the process, it touched off the social turmoil that burst into civil war, according to a study published in March 2016 in *the Proceedings of the National Academy of Sciences USA*. A dozen farmers and former business owners like Ali with whom I spoke in November 2015 at camps for Syrian refugees say that's exactly what happened.

The camp where I meet Ali, called Pikpa, is a gateway to Europe for asylum seekers who survive the perilous sea crossing from Turkey. He and his family, along with thousands of other fugitives from Syria's devastated farmlands, represent what threatens to become a worldwide crush of refugees from countries where unstable and repressive governments collapse under pressure from a toxic mix of climate change, unsustainable farming practices and water mismanagement.

40 YEARS OF FURY

SYRIA'S WATER CRISIS is largely of its own making. Back in the 1970s, the military regime led by President Hafez al-Assad launched an ill-conceived drive for agricultural self-sufficiency. No one seemed to consider whether Syria had sufficient groundwater and rainfall to raise those crops. Farmers made up for water shortages by drilling wells to tap the country's underground water reserves. When water tables retreated, people dug deeper. In 2005 the regime of Assad's son and successor, President Bashar al-Assad, made it illegal to dig new wells without a li-

IN BRIEF

Drought, which is being exacerbated by climate change and bad government policies, has forced more than a million Syrian farmers to move to overcrowded cities. Water shortages, ruined land and corruption, they say, fomented revolution.

Lack of work, along with ensuing violence, has prompted many Syrians to flee to Turkey and then cross the ocean to Greece. Hundreds of adults and children have drowned along the way.

Climate scientists say Syrian droughts will become more frequent and severe, a trend that could expand across the Middle East and the Mediterranean region.

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1

2

3

REFUGEES WHO SURVIVE the seas are often overwhelmed with relief on reaching the Greek island of Lesbos (*1* and *2*). Kemal Ali, 54, rests at the Pikpa refugee camp there (*3*). He dug wells for farmers until drought caused the water to sink too far underground, then lost use of his legs when a bus he was riding in Syria was hit by cross fire.

cense issued personally, for a fee, by an official—but it was mostly ignored, out of necessity. "What's happening globally—and particularly in the Middle East—is that groundwater is going down at an alarming rate," says Colin Kelley, then at the University of California, Santa Barbara, the *PNAS* study's lead author. "It's almost as if we're driving as fast as we can toward a cliff."

Syria raced straight over that precipice. "The war and the drought, they are the same thing," says Mustafa Abdul Hamid, a 30-year-old farmer from Azaz, near Aleppo. He talks with me on a warm afternoon at Kara Tepe, the main camp for Syrians on Lesbos. Next to an outdoor spigot, an olive tree is draped with drying baby clothes. Two boys run among the rows of tents and temporary shelters as they play a game of war, with sticks for imaginary guns. "The start of the revolution was water and land," Hamid says.

Life was good before the drought, Hamid recalls. Back home in Syria, he and his family farmed three hectares of topsoil so rich it was the color of henna. They grew wheat, fava beans, tomatoes and potatoes. Hamid says he used to harvest three

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quarters of a metric ton of wheat per hectare in the years before the drought. Then the rains failed, and his yields plunged to barely half that amount. "All I needed was water," he says. "And I didn't have water. So things got very bad. The government wouldn't allow us to drill for water. You'd go to prison."

For a while, Ali was luckier than Hamid: he had connections. As long as he had a sack full of cash, he could go on digging with no interference. "If you bring the money, you get the permissions you need fast," he explains. "If you don't have the money, you can wait three to five months. You have to have friends." He manages a smile, weakened by his condition. His story raises another long-standing grievance that contributed to Syria's downfall: pervasive official corruption.

Syrians generally viewed thieving civil servants as an inevitable part of life. After more than four decades under the two Assad family totalitarian regimes, people were resigned to all kinds of hardship. But a critical mass was developing. In recent years Iraqi War refugees and displaced Syrian farmers have inundated Syria's cities, where the urban population ballooned from 8.9 million in 2002, just before the U.S. invasion of Iraq, to 13.8 million in 2010, toward the end of the drought. What it meant for the country as a whole was summarized in the *PNAS* study: "The rapidly growing urban peripheries of Syria, marked by illegal settlements, overcrowding, poor infrastructure, unemployment and crime, were neglected by the Assad government and became the heart of the developing unrest."

By 2011 the water crisis had pushed those frustrations to the limit. "Farmers could survive one year, maybe two years, but after three years their resources were exhausted," says Richard Seager, one of the *PNAS* study's co-authors and a professor at Columbia University's Lamont-Doherty Earth Observatory. "They had no ability to do anything other than leave their lands."

Hamid agrees: "The drought lasted for years, and no one said anything against the government. Then, in 2011, we had had enough. There was a revolution." That February the Arab Spring uprisings swept the Middle East. In Syria, protests grew, crackdowns escalated and the country erupted with 40 years of pent-up fury.

NO FARMING, NO FUTURE

THIS YEAR Hamid had to abandon his family's farm. The violence had become too much for him. "I left Syria because of the war and because there was no work," he says.

Ali likewise tried to stick it out, but few of his former customers could afford to drill as deep as the water had sunk. And the war made ordinary activities practically impossible. His home village was only a short distance from the wreckage of Kobane on the Turkish border. That town was in ruins by the time the Kurds succeeded in recapturing it from ISIS, the militant group that has been terrorizing the region. In July 2015 he headed for Syria's capital, Damascus, hoping to find work and a place where his family could be safe. He was on his way there by bus when a rocket struck the vehicle. He awoke in a Damascus hospital, paralyzed from the waist down. The blast had peppered his spine with shrapnel. Somehow his family managed to get him back north, and together they made their way across Turkey to the shores of the Aegean.

Desperate strangers of all ages gather along the Turkish coast every day, not only from Syria but from all over the Middle East. They crowd onboard big rafts and set out for the roughly 16-kilometer crossing to Lesbos. The boats are routinely overloaded, and in rough seas they are easily swamped. Most cannot swim, and 20 percent are children. Drownings happen all the time.

Many do reach Lesbos alive, and they move on as quickly as possible. On the island's northern beaches the first rays of sunrise illuminate discarded orange life vests and broken boats as far as the eye can see. In November 2015 alone more than 100,000 foreign migrants passed through Greece, according to the International Organization for Migration. (A stunning 776,376 migrants had arrived in Greece between January 2015 and March 2016.) A bobbing orange dot on the horizon foretells the imminent arrival of yet another boat from Turkey. Nearing shore, one man stands up among the huddled passengers and raises his arms in triumph, flashing V-for-victory peace signs with both hands.

Louy al-Sharani, a 25-year-old from Damascus, splashes ashore with his older brother. They set off at a fast pace, carrying their bags up the steep coastal road. They both want to reach Norway

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MANY ESCAPEES from Syria cross into Turkey and travel to the western coast, where they crowd onto rafts destined for Lesbos (*map*). While at the Kara Tepe transit camp, refugees pray, bide their time and try to stay warm as they wait to go to Mytilene, the main port and capital of Lesbos (*photographs*). Once there they can buy ferry tickets to Athens and continue their journey through mainland Europe.

as soon as possible. The brother is in a hurry to find work so he can bring his wife over before summer, when the couple's first child is due. Al-Sharani says he is eager to start earning his second master's degree. "I was born to use my mind," he says. "I wasn't born to hold a machine gun and shoot people."

Their mother sold all her jewelry, including her wedding ring, to give them $6,000 for the trip. They've already spent $2,400 to get this far, al-Sharani says. Still, what choice do they have? Before the war, Sharani earned a master's in agricultural economics, but now he sees no future in Syria for himself or for the country's farmers. As if the long-term drought wasn't bad enough, ISIS has made the country's prospects even more hopeless. He claims that warring factions are now stealing wheat reserves, in effect using food as a weapon to control populations. "A farmer today can't find water to irrigate, can't find government support, and always the rebels or the Syrian army is putting pressure on him. There are a million ways to die in Syria, and you can't imagine how ugly they are," he says. "After 10 years, what I see, unfortunately, is a new Afghanistan."

(IN)FERTILE CRESCENT

COLUMBIA'S SEAGER isn't quite so pessimistic. The refugee crisis will eventually subside, he assumes, and the war in Syria will run its course. Nevertheless, he says, the region's droughts will be more frequent and more severe for the foreseeable future. After closely studying dozens of climate models, he and Kelley and their colleagues are convinced that continued greenhouse gas emissions will widen the Hadley cell, the band of air that envelops the earth's tropics in a way that could further desiccate the lands of the eastern Mediterranean.

In fact, Seager says, the Fertile Crescent could lose its current shape and might cease to exist entirely by the end of this century because of severely curtailed water flow in the Euphrates and Jordan rivers. "There's not a lot of precipitation there, and when it does shift, it makes a difference," he warns. "There's something specific about the Mediterranean that is making it hydrologically very sensitive to rising greenhouse gases."

Having gotten out, Ali and his family are trying to somehow get him to Germany, where they hope surgeons will be able to restore his ability to walk. Outdoors in his chair to get a few minutes of sun, Ali is thinking of the friends he left behind in Syria. "The life of a farmer has always been hard," he says. "Their biggest problem was water—period. Because water is life."

His son wheels him indoors for a rest. Weak winter sunlight partially illuminates a big room lined with a couple of dozen beds. Plastic sacks and cheap duffle bags are heaped everywhere, holding their owners' few remaining possessions. As Ali's children lift him into bed, his face crumples in pain and exhaustion. Fardous, his 19-year-old daughter, tucks his colostomy bag against his body and arranges the donated blankets to cover him. "It is written in the Quran," Ali repeats. "Water is life." SA

John Wendle is a freelance writer, photographer and videographer who has covered unrest in the former Soviet Union and Afghanistan since 2005. He is now examining the conflict between humans and the environment. You can see more of his work at http://johnwendle.com and https://instagram.com/johnwendle

MORE TO EXPLORE

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Map by Mapping Specialists

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EARTH SCIENCE

A History in Layers

Humans are profoundly altering the earth. Is our impact enough to matter across geologic time? Some say it is. Welcome to the Anthropocene

By Jan Zalasiewicz

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Photograph by Andrew Myers

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THE IDEA WAS BORN IN MEXICO, IN THE YEAR 2000. IT WAS PURE improvisation, by Paul Crutzen, one of the world's most respected scientists. The Dutch scholar was widely known for arguing that all-out atomic war would trigger a "nuclear winter" lethal to plant and animal life across the earth, and he had won a Nobel Prize for research into another global threat: human-caused destruction of the earth's ozone layer.

In Mexico he was listening to experts discuss evidence for changes in the global environment that had occurred throughout the Holocene, a distinct epoch that geologists say began 11,700 years ago and continues today. Growing visibly more frustrated, he burst out: "No! We are no longer in the Holocene. We are in"—he paused to think—"the Anthropocene!"

The room went silent. The term had apparently hit home. And it kept coming up, again and again, for the rest of the meeting. That year Crutzen co-wrote an article with Eugene Stoermer (since deceased), a specialist in microscopic algae called diatoms who had independently coined the term "Anthropocene" some years earlier. The evidence, the two men said in the article, was clear: industrialized humanity had changed the composition of the earth's atmosphere and oceans and had modified the landscape and biosphere—including diatom populations. We were living on a new human-driven earth, quite different from the old one. Spurred by Crutzen's prestige and vivid, persuasive writing, the concept spread rapidly among the thousands of scientists in the International Geosphere-Biosphere Program, which had sponsored the Mexico meeting. "The Anthropocene" began to appear in scientific papers around the world.

But was this really *geologic* change—change so profound that its signals are imprinted into geologic strata across the planet? Could humans really wreak change as dramatic as the transformations that started the Holocene 11,700 years ago, when extensive glaciers covering much of the earth were retreating, melting so much they raised sea level globally by 120 meters? Were human influences on the dirt beneath our feet as significant as when the Pleistocene epoch began, 2.6 million years ago, as the Ice Age tightened its grip? Could human effects only a few centuries old truly be measured alongside the great shifts of our planet's tumultuous geologic past, where time units are measured in millions—and even billions—of years?

The idea had appeared before. In the 19th and early 20th centuries scholars such as Italian cleric Antonio Stoppani and American naturalist Joseph LeConte floated terms such as Anthropozoic and Psychozoic, but geologists were dismissive, even scathing. How could human activity—no matter how impressive—compare with profound changes such as the creation and destruction of entire oceans and mountain ranges, massive volcanic eruptions and monstrous collisions by incoming meteorites? Against such a scale, human actions appeared fleeting and ephemeral.

There was another problem, too. Geologic terms such as Jurassic, Cretaceous, Pleistocene and Holocene are not just labels. They are formal names that are part of a complex geologic timescale that fundamentally characterizes how the earth evolved, thrived and struggled over 4.6 billion years. The names were ac-

IN BRIEF

Humans have altered the earth's systems, yet scientists are debating whether the changes will leave permanent signatures in geologic layers of rock, which define formal epochs and eras.

We have spread aluminum, plastics, concrete, carbon particulates (from burning fossil fuels), insecticides and radioactive particles (released by the explosion of nuclear bombs) widely across the landscape and oceans—all evidence favoring the declaration of a new Anthropocene epoch.

Questions remain about whether such an epoch would have begun thousands of years ago, when human impacts were first discernible, or may only begin at some future time, when the full impact of humans will have played out.

PRECEDING PAGES: PROP STYLING BY ANGELA CAMPOS *Stockland Martel*;

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HUMANS are paving paradise, transforming the planet's strata and defining a new geologic epoch: the Anthropocene.

GETTY IMAGES

cepted only after decades of evidence gathering and discussion by the International Commission on Stratigraphy. "Epochs" and the "eras" they belong to have specific technical meanings, and geologists take them seriously. Declaring a new epoch would imply that scientists believe humans were altering the course of the earth's evolution.

The Anthropocene had gone through none of the usual assessments. And esteemed as Crutzen is, he was an atmospheric chemist working on environmental stresses, not a geologist who was an expert in rock strata. Yet by 2008 members of the Stratigraphy Commission of the Geological Society of London realized that the term was increasingly being used in the literature as if it *were* a formal epoch. The society decided it had to confront the trend.

This cautious and conservative group meets in the old-world

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Council Room in London's Burlington House, complete with solemn portraits on the walls, where Victorian giants of the sciences such as Charles Darwin once walked. In this heavily traditional setting, the scientists began the geologic assessment of the Anthropocene. Perhaps to their own surprise, most of them agreed that the term "had merit" as a potentially formal unit of the proper geologic time scale and should be examined. Geologist Philip Gibbard, who also chaired the International Commission on Stratigraphy's Subcommission on Quaternary Stratigraphy—which has power over the geologic timescale—proposed a working group that has been exploring the question ever since.

To make a case, scientists must show that human impacts will leave a clear mark, fossilized in strata, that could be readily recognized tens or hundreds of millions of years from now by some geologist in the far future. The focus on strata is important. To a geologist, geologic strata *equal* geologic time. The key is a "time-rock" interval—a layer of strata that can be hammered, sampled or dug in (as for dinosaur bones) and that defines a new course of history. For the Anthropocene epoch to have such deep geologic meaning and to have any chance of being made formal, it must show its own time-rock unit. Is there enough evidence to pass muster? One could make a good case.

1

ULET IFANSASTI Getty Images

ROCKS AND 'OIDS

LET'S START WITH MINERALS, the fundamental components of rocks. Metals, for example, are almost always bound up in various oxides, carbonates and silicates (with rare exceptions such as gold). Humans have learned to separate metals out of these compounds, in huge quantities. We have manufactured more than 500 million metric tons of aluminum since World War II, enough to coat the entire U.S. in kitchen foil. As we scatter billions of cans, appliances, cigarette pack liners and other refuse across the landscape and into landfills, pure aluminum is becoming part of modern sediment layers.

The last great rise in mineral forms occurred about 2.5 billion years ago, when the earth's atmosphere became oxygenated. The event produced an array of oxides and hydroxides, including rust—which, incidentally, changed the color of the landscape from gray to red. But humans have now created another great rise by synthesizing many mineral compounds, such as tungsten carbide, common in tools and ballpoint pens. Perhaps the most striking inventions are "mineraloids" such as glasses and plastics. Before WWII plastics were limited to a few products such as shellac, Bakelite and rayon, but after the war they rocketed to the 300 million metric tons now made annually—roughly equivalent to the total human body mass. The qualities we find so useful in plastics—durability and resistance to decay—mean that they persist in the environment for many years.

The signature of plastic litter in the ground is strong enough, but it is even more geologically significant in the oceans. Because many sea creatures eat plastics, much of it ends up in the muds of the seafloor when the animals die—a first step to fossilization. Invisible to our eyes but more pervasive still are microplastics, such as the fibers detached from synthetic clothes. Even on remote ocean floors, far from land, researchers are finding thousands of fibers in every square meter of mud.

Human-made rocks are everywhere, too. For sheer bulk, concrete now reigns supreme; we have manufactured something like half a trillion metric tons to date. That is about a kilogram of concrete for every square meter of the earth's surface. Concrete forms the superstructures of our buildings, roads and dams, and broken-up fragments are now common in the turned-over ground underneath our towns and cities. It is already a signature rock of the Anthropocene, together with human-made bricks and ceramics. The enormous masses of the rocks we make impregnate the top part of the earth's crust, which we are also redistributing as big machines dig and plow soil to construct buildings and grow food. Humans now shift more sediment than natural forces such as rivers and wind do.

CHEMICAL FINGERPRINTS

IN THE PAST CENTURY or so, the burning of fossil fuels has largely powered the accelerated production and planetary de-

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MOUNTAINS of plastics in Jakarta (*1*) and of concrete in New York City (*2*) will persist long enough to permanently impregnate the earth's crust.

position of new strata materials such as aluminum, plastic and concrete. The by-products of combustion are themselves so voluminous that they, too, leave a variety of chemical signals in sediments worldwide. The rise of carbon dioxide in the atmosphere since the industrial revolution began is about 100 times faster than the rate of rise when the glaciers retreated at the start of the Holocene. The emissions are captured and recorded in bubbles of air trapped in layer on layer of snow and ice frozen in the world's polar caps.

Combustion also produces smoke—incompletely burned particles that are tiny and inert. Falling to the ground worldwide, they form a geologically lasting smoke signal. The fires ignited by the meteorite impact that defines the boundary between the Cretaceous and Tertiary intervals left a similar trace in the rocks. The carbon from burned fossil fuels is also distinctly rich in the light carbon 12 isotope (^{12}C), which plants and animals readily absorb. As these life-forms die, they will be fossilized, leaving a permanent ^{12}C mark of the Anthropocene.

Widespread agriculture is casting its own chemical shadow. Humankind started farming about 10,000 years ago, but only since the early 1900s have farmers applied vast quantities of nitrogen fertilizer, extracted from the air by a technique known as the Haber-Bosch process, together with phosphorus dug from the ground. The enormous perturbations in soil, water and air leave clear chemical signatures. Lakes at high latitudes become polluted by these compounds, blown in by winds from distant farming regions. Fertilizer runoff from farm fields into streams and rivers and out to the sea overstimulates plankton production; as the huge blooms die and decay, they create "dead zones" that now suffocate seafloor life over hundreds of thousands of square kilometers every year. The devastated marine biology will tell its story as fossils in future strata.

Other chemical signals include persistent organic pollutants such as insecticides and toxic industrial chemicals such as dioxins, which now contaminate many sediments. Some of these may persist over geologic timescales, as did the long-chain carbon compounds produced by some ancient algae that paleontologists now use as tracers of climate tens of millions of years ago.

Tiny radioactive particles that spread around the globe after every nuclear bomb explosion are also detectable. Although only a couple of such bombs were dropped as part of war, various countries detonated more than 500 test bombs in the atmosphere between the mid-1940s and the late 1990s. The particles fell into soil, polar ice and seafloor sediment alike, and they were absorbed by animals and plants at the surface. This radioactive layer is one of the most abrupt Anthropocene signatures.

FOSSIL TRANSITIONS

WE HUMANS have obviously left our mark on the earth's biological landscape as well. In particular, our species—a very minor player amid the planet's biota even a few thousand years ago—is now the dominant predator on land and sea. We appropriate

GEORGE HAMMERSTEIN *Getty Images*

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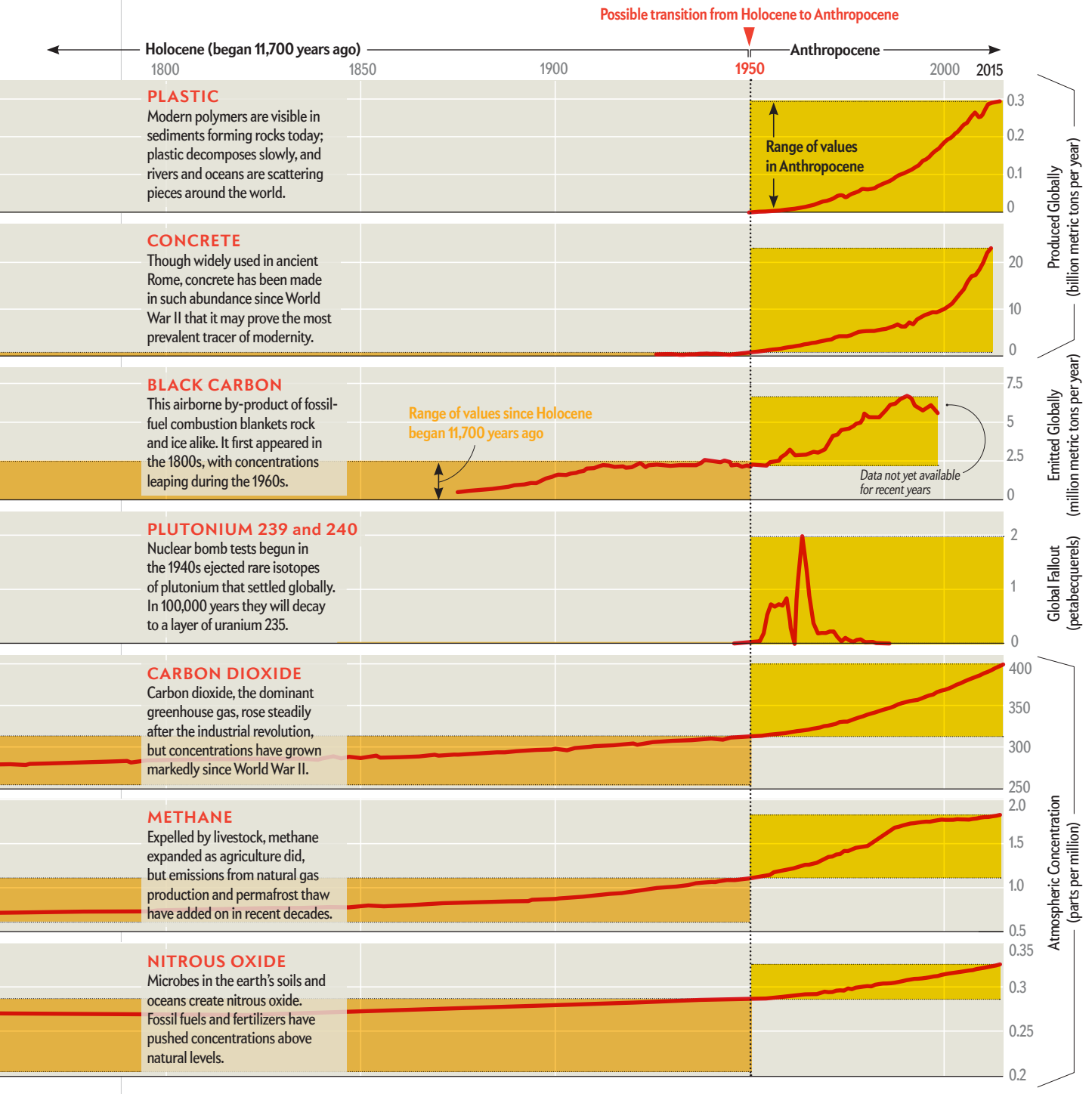
TIMELINE

When Did the Anthropocene Begin?

The detritus of modern humanity is so pervasive that our "techno-fossils"—such as plastic and concrete—will permeate the rock that is forming today. Mounting evidence collected by scientists supports the idea that human activity has pushed the planet into a new geologic epoch: the Anthropocene. They say the epoch will prove distinct from the Holocene, which began when glaciers retreated 11,700 years ago—and that 1950 may be the logical threshold between the two. Markers of the Anthropocene (*shown below*) have spread across the globe, says Colin Waters of the British Geological Survey. "We've in effect become a new geologic force." —*Katie Peek*


Possible transition from Holocene to Anthropocene
Holocene (began 11,700 years ago)
Anthropocene
1800
1850
1900
1950
2000
2015
PLASTIC
Modern polymers are visible in sediments forming rocks today; plastic decomposes slowly, and rivers and oceans are scattering pieces around the world.
Range of values in Anthropocene
0.3
0.2
0.1
0
CONCRETE
Though widely used in ancient Rome, concrete has been made in such abundance since World War II that it may prove the most prevalent tracer of modernity.
20
10
0
Produced Globally (billion metric tons per year)
BLACK CARBON
This airborne by-product of fossil-fuel combustion blankets rock and ice alike. It first appeared in the 1800s, with concentrations leaping during the 1960s.
Range of values since Holocene began 11,700 years ago
Data not yet available for recent years
7.5
5
2.5
0
Emitted Globally (million metric tons per year)
PLUTONIUM 239 and 240
Nuclear bomb tests begun in the 1940s ejected rare isotopes of plutonium that settled globally. In 100,000 years they will decay to a layer of uranium 235.
2
1
0
Global Fallout (petabecquerels)
CARBON DIOXIDE
Carbon dioxide, the dominant greenhouse gas, rose steadily after the industrial revolution, but concentrations have grown markedly since World War II.
400
350
300
250
METHANE
Expelled by livestock, methane expanded as agriculture did, but emissions from natural gas production and permafrost thaw have added on in recent decades.
2.0
1.5
1.0
0.5
NITROUS OXIDE
Microbes in the earth's soils and oceans create nitrous oxide. Fossil fuels and fertilizers have pushed concentrations above natural levels.
0.35
0.3
0.25
0.2
Atmospheric Concentration (parts per million)

SOURCES: "THE ANTHROPOCENE IS FUNCTIONALLY AND STRATIGRAPHICALLY DISTINCT FROM THE HOLOCENE," BY COLIN N. WATERS ET AL., IN *SCIENCE*, VOL. 351; JANUARY 8, 2016; AND REFERENCES CONTAINED THEREIN; U.S. ENVIRONMENTAL PROTECTION AGENCY

Graphic by Katie Peek

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roughly a quarter of the earth's total biological production for our needs. As a result, we make up about a third of the mass of all land vertebrates (based simply on body weight), and the handful of animal species we have engineered to become our food make up most of the other two thirds. Wild animals, pushed to the margins, constitute 5 percent or less. In colonizing so much of the planet's land, we have comprehensively reshuffled what is left of wildlife, too, purposely or accidentally transporting animals and plants across the globe, homogenizing biology worldwide. We are also killing so many species that in another century or two the planet's biodiversity could take as catastrophic a hit as the one that happened when the dinosaurs disappeared. These transformations will show up in the distant future as a switch from one assemblage of fossils to another.

Humans have meanwhile taken the manufacture of "trace fossils"—such as footprints by dinosaurs and burrows by sea worms—to completely new levels. Our mines and boreholes penetrate several kilometers into the ground, so deep that these traces permanently scar the planet. The towns and cityscapes that have made over the earth's surface are also mirrored in subsurface foundations, pipelines and subway systems.

PERMANENT OR FLEETING?

ALL IN ALL, we humans have left a formidable catalog of new geologic signatures. Will these effects *permanently* reconfigure the earth's strata and future history, defining a formal new epoch? Or, with humans gone, will the earth system spring back to normal, eroding our constructions into dust, like the fate of the mighty Ozymandias empire in Percy Bysshe Shelley's poem of the same name? It is still early days.

Luckily, four billion years of strata have left us a few lessons. Where the earth's crust is rising, such as on growing mountain ranges, surface structures are indeed eroded and washed away as sedimentary particles into some far-off sea. Where the crust is subsiding—as below many of the world's major deltas—the strata piling up can preserve even seemingly ephemeral traces, such as leaves, twigs and footprints. Therefore, San Francisco, pushed up by tectonic forces, seems destined to be weathered away. Sinking New Orleans, Shanghai and Amsterdam, however, will leave ample traces of their massive, complex structures, together with aluminum, plastic, ceramics—and skeletons with metal-filled teeth and artificial hips. When these strata are ultimately pushed up high by tectonic forces, millions of years from now, the newly minted cliffs will reveal a distinctive Anthropocene layer.

The permanence of fossils, and of long-term consequences of our actions, figures in the answer, too. The meteorite strike that ended the Cretaceous period was instantaneous; the immediate shock wave was over in hours. But its effects reshaped biology for millions of years, and the reverberations are still with us today. Without that meteorite we might not be here now; dinosaurs might still be ruling the earth.

Humanity's impact, swift though not that sudden, could likewise change the planet in ways that will be felt long after we disappear. Many trends are accelerating, and some—species extinction, climate change and sea-level rise—are only in their early stages. Regardless of when the fossil-fuel era finally ends, its effects will diminish only slowly, over many millennia. (And human civilization, which developed in the environmentally stable Holocene, will have to adapt to an unstable, changing planet for many generations.)

We may exert a long-term influence in another way as well. Humanity is a much more complex, protean planetary force than a meteorite strike or glacial retreat. Our extraordinary geologic power is driven by our intelligence, our manipulative ability and our hypersocial interactions that pass on new knowledge. These traits have allowed us to develop the technology that now keeps us alive, and that itself is evolving at an accelerating rate, literally from year to year.

This emergent technosphere, as Duke University professor emeritus Peter Haff calls it, can be considered an outgrowth of the biosphere. It has its own dynamics, over which we have only partial control. It includes the possibility that a silicon-based intelligence could soon vie with our own. Among all the ongoing global changes that will determine the geologic future of the earth, the technosphere is the wild card. It could produce a revised Anthropocene planetary state—only humans may no longer be calling the shots. For now scientists can decide only how to characterize the present. Should an earth that is rapidly, profoundly and permanently being transformed by humans be formally recognized in a new epoch in the geologic timescale?

For the geologists who would make the determination, the jury is still out. Important decisions need to be made. When would the Anthropocene have begun, for instance? Suggestions have ranged from thousands of years ago, when human impacts first became discernible, to far into the future, once our impacts are fully expressed. For practical purposes, the most suitable boundary seems to be the extraordinary "great acceleration" of population, energy use and industrialization begun in the mid-1900s. Strata after that time are marked by strong rises in concrete, plastics, plutonium and the remains of a transformed biology.

Geologists are searching for a suitable "golden spike"—a carefully selected reference that serves as a global marker for a new epoch. Would that be provided by the radioactive nuclei or carbon particles trapped in the snow and ice layers of Greenland and Antarctica, in sediment layers in far-flung lakes and fjords, and on undisturbed seafloors? Or might it be some other indicator, a telltale change in living chemistry preserved within tree rings and annual coral growth bands? The hunt is on. SA

Jan Zalasiewicz is a professor of paleobiology at the University of Leicester in England and is chair of the Anthropocene Working Group of the International Commission on Stratigraphy. He has a particular fondness for graptolites—an extinct form of plankton.

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scientificamerican.com/magazine/sa

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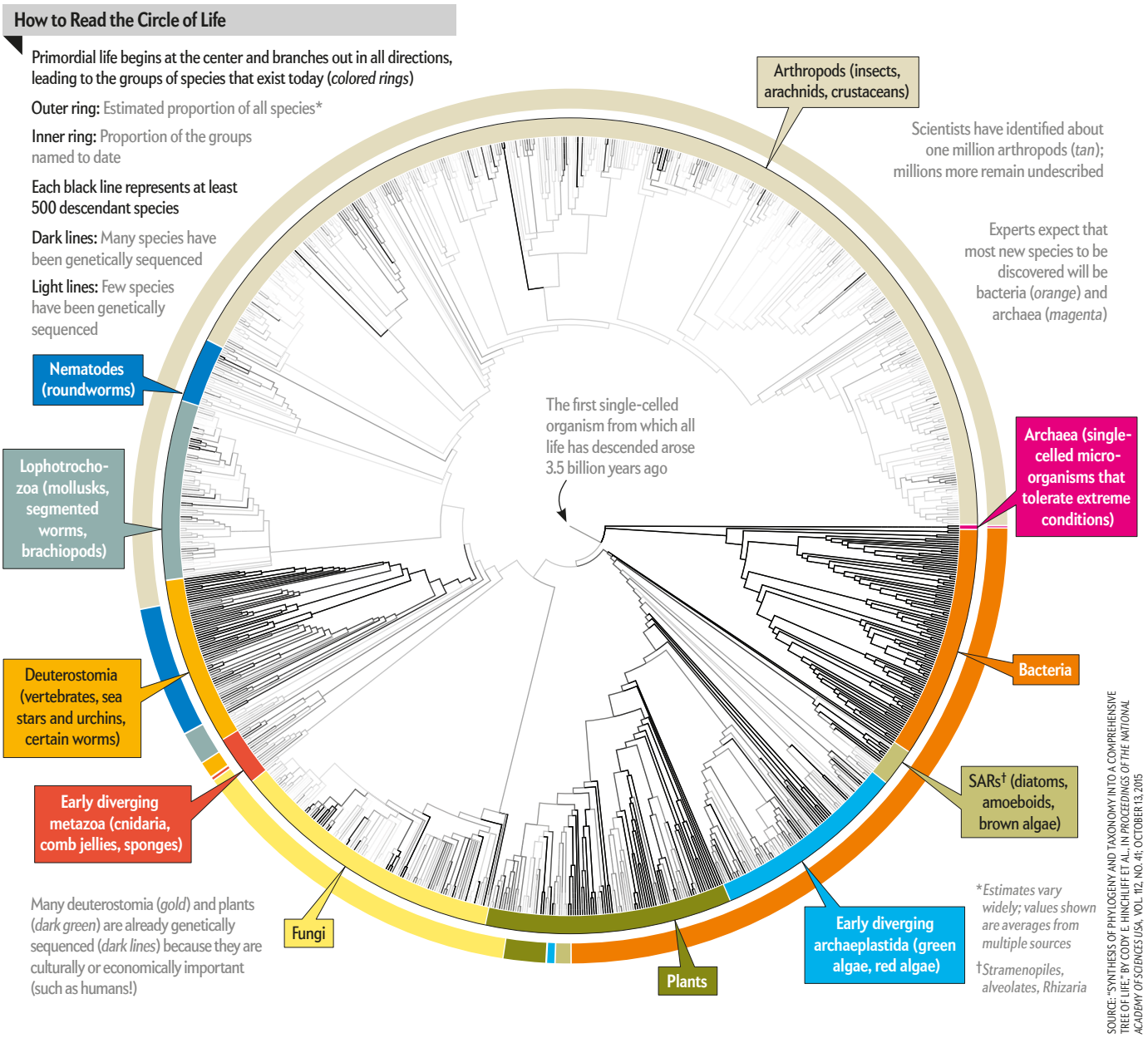
END NOTE

The Circle of Life

Lineages of all known species on earth are finally pieced together

Since Charles Darwin's day, biologists have depicted how new organisms evolve from old ones by adding branches to numerous trees that represent portions of the animal, plant and microbial kingdoms. Researchers from a dozen institutions recently completed a three-year effort to combine tens of thousands of trees into one diagram, most readable as a circle (*below*). The lines inside the circle represent all 2.3 million species that have been named. Biologists have genetic sequences for only about 5 percent of them, however; as more are finished, the relationships within and across groups of species may change. Experts estimate that up to 8.7 million species may inhabit the planet (about 15,000 are discovered every year). "We expect the circle to broaden," says Karen Cranston, a computational evolutionary biologist at Duke University.

Anyone can propose updates to the database (OpenTreeOfLife.org). Greater detail could improve understanding of evolution and help scientists invent drugs, make crops more productive and better control infectious diseases. —*Mark Fischetti*


How to Read the Circle of Life
Primordial life begins at the center and branches out in all directions, leading to the groups of species that exist today (colored rings)
Outer ring: Estimated proportion of all species*
Inner ring: Proportion of the groups named to date
Each black line represents at least 500 descendant species
Dark lines: Many species have been genetically sequenced
Light lines: Few species have been genetically sequenced
Arthropods (insects, arachnids, crustaceans)
Scientists have identified about one million arthropods (tan); millions more remain undescribed
Experts expect that most new species to be discovered will be bacteria (orange) and archaea (magenta)
Nematodes (roundworms)
Lophotrocho-zoa (mollusks, segmented worms, brachiopods)
Deuterostomia (vertebrates, sea stars and urchins, certain worms)
Early diverging metazoa (cnidaria, comb jellies, sponges)
The first single-celled organism from which all life has descended arose 3.5 billion years ago
Archaea (single-celled micro-organisms that tolerate extreme conditions)
Bacteria
SARs† (diatoms, amoeboids, brown algae)
Early diverging archaeplastida (green algae, red algae)
Plants
Fungi
Many deuterostomia (gold) and plants (dark green) are already genetically sequenced (dark lines) because they are culturally or economically important (such as humans!)
*Estimates vary widely; values shown are averages from multiple sources
†Stramenopiles, alveolates, Rhizaria
SOURCE: "SYNTHESIS OF PHYLOGENY AND TAXONOMY INTO A COMPREHENSIVE TREE OF LIFE," BY CODY E. HINCHLIFF ET AL., IN PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA, VOL. 112, NO. 41; OCTOBER 13, 2015

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BRIGHT HORIZONS 33

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- Paper-making and Printing
- Gunpowder and Cannons
- The Compass and Celestial Navigation

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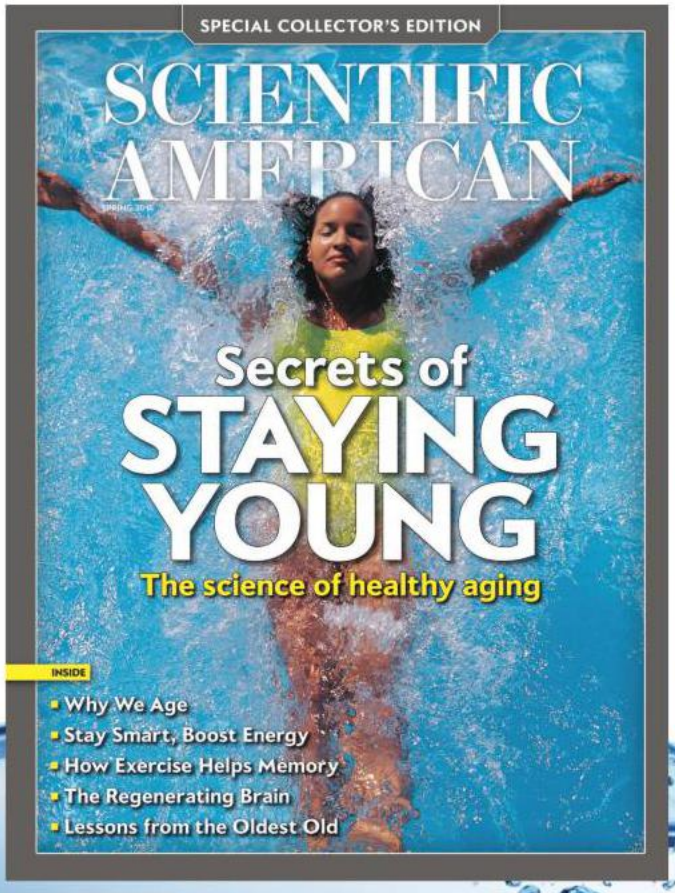

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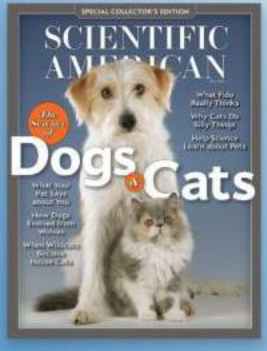

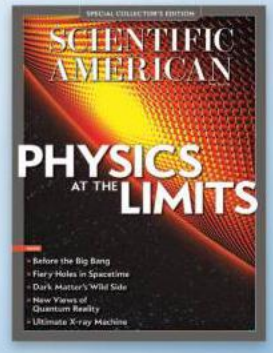

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